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(54) Title: HETEROPOLYCYCLIC COMPOUNDS AND THEIR USE AS METABOTROPIC GLUTAMATE RECEPTOR ANTAGONISTS

(57) Abstract: The present invention provides compounds and pharmaceutical compositions that act as antagonists at metabotropic glutamate receptors, and that are useful for treating neurological diseases and disorders. Method of preparing the compounds also are disclosed.

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HETEROPOLYCYCLIC COMPOUNDS AND THEIR USE AS METABOTROPIC GLUTAMATE RECEPTOR ANTAGONISTS

CROSS-REFERENCE TO RELATED PATENT APPLICATIONS

This application claims priority to U.S. Provisional Application Ser. No. 60/269,847, filed 02/21/2001.

FIELD OF THE INVENTION

The present invention provides compounds that are active at metabotropic glutamate receptors, particularly compounds that are active as antagonists at metabotropic glutamate receptors, more particularly at the mGluR5 glutamate receptor.

BACKGROUND OF THE INVENTION

Recent advances in the elucidation of the neurophysiological roles of metabotropic glutamate receptors have established these receptors as promising drug targets in the therapy of acute and chronic neurological and psychiatric disorders and diseases. However, the major challenge to the realization of this promise has been the development of metabotropic glutamate receptor subtype-selective compounds.

Glutamate is the major excitatory neurotransmitter in the mammalian central nervous system (CNS). Glutamate produces its effects on central neurons by binding to and thereby activating cell surface receptors. These receptors have been divided into two major classes, the ionotropic and metabotropic glutamate receptors, based on the structural features of the receptor proteins, the means by which the receptors transduce signals into the cell, and pharmacological profiles.

The metabotropic glutamate receptors (mGluRs) are G protein-coupled receptors that activate a variety of intracellular second messenger systems following the binding of glutamate. Activation of mGluRs in intact mammalian neurons elicits one or more of the following responses: activation of phospholipase C; increases in phosphoinositide (PI) hydrolysis; intracellular calcium release; activation of phospholipase D; activation or inhibition of adenyl cyclase; increases

or decreases in the formation of cyclic adenosine monophosphate (cAMP); activation of guanylyl cyclase; increases in the formation of cyclic guanosine monophosphate (cGMP); activation of phospholipase A_2; increases in arachidonic acid release; and increases or decreases in the activity of voltage- and ligand-gated ion channels. Schoepp *et al.*, *Trends Pharmacol. Sci. 14*:13 (1993); Schoepp, *Neurochem. Int. 24*:439 (1994); Pin *et al.*, *Neuropharmacology 34*:1 (1995).

Eight distinct mGluR subtypes, termed mGluR1 through mGluR8, have been identified by molecular cloning. *See, for example,* Nakanishi, *Neuron 13*:1031 (1994); Pin *et al.*, *Neuropharmacology 34*:1 (1995); Knopfel *et al.*, *J. Med. Chem. 38*:1417 (1995). Further receptor diversity occurs via expression of alternatively spliced forms of certain mGluR subtypes. Pin *et al.*, *PNAS 89*:10331 (1992); Minakami *et al.*, *BBRC 199*:1136 (1994); Joly *et al.*, *J. Neurosci. 15*:3970 (1995).

Metabotropic glutamate receptor subtypes may be subdivided into three groups, Group I, Group II, and Group III mGluRs, based on amino acid sequence homology, the second messenger systems utilized by the receptors, and by their pharmacological characteristics. Nakanishi, *Neuron 13*:1031 (1994); Pin *et al.*, *Neuropharmacology 34*:1 (1995); Knopfel *et al.*, *J. Med. Chem. 38*:1417 (1995).

Group I mGluRs comprise mGluR1, mGluR5, and their alternatively spliced variants. The binding of agonists to these receptors results in the activation of phospholipase C and the subsequent mobilization of intracellular calcium. Electrophysiological measurements have been used to demonstrate these effects, for example, in *Xenopus* oocytes that express recombinant mGluR1 receptors. *See, for example,* Masu *et al.*, *Nature 349*:760 (1991); Pin *et al.*, *PNAS 89*:10331 (1992). Similar results have been achieved with oocytes expressing recombinant mGluR5 receptors. Abe *et al.*, *J. Biol. Chem. 267*:13361 (1992); Minakami *et al.*, *BBRC 199*:1136 (1994); Joly *et al.*, *J. Neurosci. 15*:3970 (1995). Alternatively, agonist activation of recombinant mGluR1 receptors expressed in Chinese hamster ovary (CHO) cells stimulates PI hydrolysis, cAMP formation, and arachidonic acid release as measured by standard biochemical assays. Aramori *et al.*, *Neuron 8*:757 (1992).

By comparison, the activation of mGluR5 receptors, expressed in CHO cells, stimulates PI hydrolysis and subsequent intracellular calcium transients, but no stimulation of cAMP formation or arachidonic acid release is observed. Abe *et al.*,

J. Biol. Chem. 267:13361 (1992). However, activation of mGluR5 receptors expressed in LLC-PK1 cells results in PI hydrolysis and increased cAMP formation. Joly *et al., J. Neurosci. 15*:3970 (1995). The agonist potency profile for Group I mGluRs is quisqualate > glutamate = ibotenate > *(2S,1'S,2'S)*-2-carboxycyclopropyl)glycine (L-CCG-I) > *(1S,3R)*-1-aminocyclopentane-1,3-dicarboxylic acid (ACPD). Quisqualate is relatively selective for Group I receptors, as compared to Group II and Group III mGluRs, but it also is a potent activator of ionotropic AMPA receptors. Pin *et al., Neuropharmacology 34*:1, Knopfel *et al., J. Med. Chem. 38*:1417 (1995).

The lack of subtype-specific mGluR agonists and antagonists has impeded elucidation of the physiological roles of particular mGluRs, and the mGluR-associated pathophysiological processes that affect the CNS have yet to be defined. However, work with the available non-specific agonists and antagonists has yielded some general insights about the Group I mGluRs as compared to the Group II and Group III mGluRs.

Attempts at elucidating the physiological roles of Group I mGluRs suggest that activation of these receptors elicits neuronal excitation. Various studies have demonstrated that ACPD can produce postsynaptic excitation upon application to neurons in the hippocampus, cerebral cortex, cerebellum, and thalamus, as well as other brain regions. Evidence indicates that this excitation is due to direct activation of postsynaptic mGluRs, but it also has been suggested that activation of presynaptic mGluRs occurs, resulting in increased neurotransmitter release. Baskys, *Trends Pharmacol. Sci. 15*:92 (1992); Schoepp, *Neurochem. Int. 24*:439 (1994); Pin *et al., Neuropharmacology 34*:1(1995).

Pharmacological experiments implicate Group I mGluRs as the mediators of this excitatory mechanism. The effects of ACPD can be reproduced by low concentrations of quisqualate in the presence of ionotrophicGluR antagonists. Hu *et al., Brain Res. 568*:339 (1991); Greene *et al., Eur. J. Pharmacol. 226*:279 (1992). Two phenylglycine compounds known to activate mGluR1, namely *(S)*-3-hydroxyphenylglycine (*(S)*-3HPG) and *(S)*-3,5-dihydroxyphenylglycine (*(S)*-DHPG), also produce excitation. Watkins *et al., Trends Pharmacol. Sci. 15*:33 (1994). In addition, the excitation can be blocked by *(S)*-4-carboxyphenylglycine (*(S)*-4CPG), *(S)*-4-carboxy-3-hydroxyphenylglycine (*(S)*-4C3HPG), and (+)-alpha-methyl-4-

carboxyphenylglycine ((+)-MCPG), compounds known to be mGluR1 antagonists. Eaton *et al., Eur. J. Pharmacol. 244*:195 (1993); Watkins *et al., Trends Pharmacol. Sci. 15*:333 (1994).

Metabotropic glutamate receptors have been implicated in a number of normal processes in the mammalian CNS. Activation of mGluRs has been shown to be required for induction of hippocampal long-term potentiation and cerebellar long-term depression. Bashir *et al., Nature 363*:347 (1993); Bortolotto *et al., Nature 368*:740 (1994); Aiba *et al., Cell 79*:365 (1994); Aiba *et al., Cell 79*:377 (1994). A role for mGluR activation in nociception and analgesia also has been demonstrated. Meller *et al., Neuroreport 4*: 879 (1993). In addition, mGluR activation has been suggested to play a modulatory role in a variety of other normal processes including synaptic transmission, neuronal development, apoptotic neuronal death, synaptic plasticity, spatial learning, olfactory memory, central control of cardiac activity, waking, motor control, and control of the vestibulo-ocular reflex. Generally, see Nakanishi, *Neuron 13*: 1031 (1994); Pin *et al., Neuropharmacology 34*:1; Knopfel *et al., J. Med. Chem. 38*:1417 (1995).

Metabotropic glutamate receptors also have been suggested to play roles in a variety of pathophysiological processes and disease states affecting the CNS. These include stroke, head trauma, anoxic and ischemic injuries, hypoglycemia, epilepsy, and neurodegenerative diseases such as Alzheimer's disease. Schoepp *et al., Trends Pharmacol. Sci. 14*:13 (1993); Cunningham *et al., Life Sci. 54*:135 (1994); Hollman *et al., Ann. Rev. Neurosci. 17*:31 (1994); Pin *et al., Neuropharmacology 34*:1 (1995); Knopfel *et al., J. Med. Chem. 38*:1417 (1995). Much of the pathology in these conditions is thought to be due to excessive glutamate-induced excitation of CNS neurons. Because Group I mGluRs appear to increase glutamate-mediated neuronal excitation via postsynaptic mechanisms and enhanced presynaptic glutamate release, their activation probably contributes to the pathology. Accordingly, selective antagonists of Group I mGluR receptors could be therapeutically beneficial, specifically as neuroprotective agents, analgesics, or anticonvulsants.

Preliminary studies assessing therapeutic potentials with the available mGluR agonists and antagonists have yielded seemingly contradictory results. For example, it has been reported that application of ACPD onto hippocampal neurons

leads to seizures and neuronal damage (Sacaan *et al., Neurosci. Lett. 139*:77 (1992); Lipparti *et al., Life Sci. 52*:85 (1993). Other studies indicate, however, that ACPD inhibits epileptiform activity, and also can exhibit neuroprotective properties. Taschenberger *et al., Neuroreport 3*:629 (1992); Sheardown, *Neuroreport 3*:916 (1992); Koh *et al., Proc. Natl. Acad. Sci. USA 88*:9431 (1991); Chiamulera *et al., Eur. J. Pharmacol. 216*:335 (1992); Siliprandi *et al., Eur. J. Pharmacol. 219*:173 (1992); Pizzi *et al., J. Neurochem. 61*:683 (1993).

It is likely that these conflicting results are due to the lack of selectivity of ACPD, which causes activation of several different mGluR subtypes. In the studies finding neuronal damage it appears that Group I mGluRs were activated, thereby enhancing undesirable excitatory neurotransmission. In the studies showing neuroprotective effects it appears that activation of Group II and/or Group III mGluRs occurred, inhibiting presynaptic glutamate release, and diminishing excitatory neurotransmission.

This interpretation is consistent with the observation that *(S)*-4C3HPG, a Group I mGluR antagonist and Group II mGluR agonist, protects against audiogenic seizures in DBA/2 mice, while the Group II mGluR selective agonists DCG-IV and L-CCG-I protect neurons from NMDA- and KA-induced toxicity. Thomsen *et al., J. Neurochem. 62*:2492 (1994); Bruno *et al., Eur. J. Pharmacol. 256*:109 (1994); Pizzi *et al., J. Neurochem. 61*:683 (1993).

Based on the foregoing, it is clear that a lack of potency and selectivity limits the value of the mGluR agonists and antagonists now available. In addition, most currently available compounds are amino acids or amino-acid derivatives which have limited bioavailabilities, thereby hampering *in vivo* studies to assess mGluR physiology, pharmacology, and therapeutic potential. On the other hand, compounds that selectively inhibit activation of metabotropic glutamate receptor Group I subtypes are indicated for treatment of neurological disorders and diseases such as senile dementia, Parkinson's disease, Alzheimer's disease, Huntington's Chorea, pain, epilepsy, head trauma, anoxic and ischemic injuries, and psychiatric disorders such as anxiety, schizophrenia and depression.

Accordingly, a need exists for potent mGluR agonists and antagonists that display a high selectivity for a mGluR subtype, particularly a Group I receptor subtype.

SUMMARY OF THE INVENTION

The present invention, provides metabotopic glutamate receptor-active compounds, which exhibit a high degree of potency and selectivity for individual metabotropic glutamate receptor subtypes, and processes of making these compounds.

Further, this invention provides pharmaceutical compositions containing compounds which exhibit a high degree of potency and selectivity for individual metabotropic glutamate receptor subtypes, and to provide methods of making these pharmaceutical compositions.

Another aspect of the invention is to provide methods of inhibiting activation of an mGluR Group I receptor, specifically mGluR5. In particular, a medical condition associated with metabotropic glutamate receptors includes: stroke; head; trauma; anoxic; injury; ischemic; injury; hypoglycemia; epilepsy; pain; migraine headaches; Parkinson's disease; senile dementia; Huntington's Chorea; and Alzheimer's disease.

The invention provides methods of treating a disease associated with excitatory activation of an mGluR Group I receptor and of inhibiting neuronal damage caused by excitatory activation of an mGluR Group I receptor, specifically wherein the mGluR Group I receptor is mGluR5 Finally, the present invention provides potent antagonists of Group I mGluRs, specifically mGluR5.

According to a first aspect of the invention, these antagonists may be represented by compounds of the general formula:

$$Ar^1\text{-}L\text{-}Ar^2$$

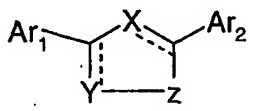
wherein Ar^1 is an optionally substituted heteroaromatic moiety and Ar^2 is an optionally substituted benzene ring. The L moiety is a group that not only covalently binds to the Ar^1 and Ar^2 moieties, and facilitates adoption of the correct spatial orientation of Ar^1 and Ar^2, but also itself may interact with the protein, to effect receptor binding.

In one embodiment of the invention, L is selected from the group consisting of -NH-, -S-, -O-, -CO-, -CONH-, -$CONHCH_2$-, -CH_2CONH-, -CNHNH-, -$CNHNHCH_2$-, -C=NO-CH_2-, -CH_2NHCH_2-, -CH_2CH_2NH-, -$NHCH_2CO$-, -$NHCH_2CHOH$-, -NHCNHNH.-

, -NHCONH-, cyclopentane, cyclopentadiene, furan, thiofuran, pyrrolidine, pyrrole, 2-imidazoline, 3-imidazoline, 4-imidazoline, imidazole, pyrazoline, pyrazolidine, imidazolidine, oxazole, 2-oxazole, thiazole, isoxazole, isothiazole, 1*H*-1,2,4-triazole, 1*H*-1,2,3-triazole, 1,2,4-oxathiazole, 1,3,4-oxathiazole, 1,4,2-dioxazole, 1,4,2-oxathiazole, 1,2,4-oxadiazole, 1,2,4-thiadiazole, 1,2,5-oxadiazole, 1,2,5-thiadiazole, 1,3,4-oxadiazole, 1,3,4-thiadiazole, 1*H*-tetrazole, cyclohexane, piperidine, tetrahydropyridine, 1,4-dihydropyridine, pyridine, benzene, tetrahydropyran, 3,4-dihydro-2*H*-pyran, 2*H*-pyran, 4*H*-pyran, tetrahydrothiopyran, 3,4-dihydro-2*H*-thiopyran, 2*H*-thiin, 4*H*-thiopyran, morpholine, thiomorpholine, piperazine, pyridazine, pyrimidine, pyrazine, 1,2,4-triazine, 1,2,3-triazine, 1,3,5-triazine, and 1,2,4,5-tetrazine.

In another embodiment of the invention, Ar^1 is selected from the group consisting of phenyl, benzyl, naphthyl, fluorenyl, anthrenyl, indenyl, phenanthrenyl, and benzonaphthenyl, and Ar^2 is selected from the group consisting of thiazoyl, furyl, pyranyl, 2H-pyrrolyl, thienyl, pyrroyl, imidazoyl, pyrazoyl, pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl, benzothiazole, benzimidazole, 3H-indolyl, indolyl, indazoyl, purinyl, quinolizinyl, isoquinolyl, quinolyl, phthalizinyl, naphthyridinyl, quinazolinyl, cinnolinyl, isothiazolyl, quinoxalinyl indolizinyl, isoindolyl, benzothienyl, benzofuranyl, isobenzofuranyl, and chromenyl.

According a second aspect of the invention, these antagonists may be represented by compounds of Formula I:



I

wherein

---- represents a double or single bond;

X, Y, and Z are independently selected from the group consisting of: N; O; S; and CR_1 and at least one of X, Y, and Z is a heteroatom;

wherein

R_1 is selected from the group consisting of: H; alkyl; $-CF_3$; $-OR_2$; $-SR_2$; $-NR_2R_3$; $=O$; $=S$; $=NR_2$; and $=CR_2R_3$; and

wherein

R_2 and R_3 may be independently selected from the group consisting of: H; alkyl; haloalkyl; alkyloxy; alkylamine; cycloalkyl; heterocycloalkyl; aryl; heteroaryl; alkylaryl; alkylheteroaryl; haloaryl; alkyloxyaryl; alkenylaryl; alkenyloxyaryl; and haloheteroaryl; and

Ar_1 and Ar_2 are independently selected from the group consisting of: aryl and heteroaryl, and at least one of Ar_1 and Ar_2 is substituted with at least one substituent G;

wherein

G is selected from the group consisting of: haloalkyl; heteroaryl; cycloalkene; alkenyl; alkynyl; A-alkenyl; A-alkynyl; alkyloxy; A-alkyloxy; -R_2OR_3; -$R_2OC(O)R_3$; -$(CH_2)_m$-NR_2R_3; -$OCH_2CH(Cl)CH_2Cl$; and substituted aryl wherein the aryl substituent is R_4, and

wherein

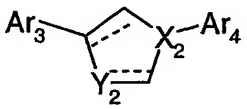
A is a linker selected from the group consisting of: CH_2; O; NH; S; SO; SO_2; NSO_2; OSO_2; and -$C(NR_2)NR_3$;

m is selected from 0 and 1; and

R_4 is selected from the group consisting of: halo; -OR_2; -SR_2; -SOR_2; -SO_2R_2; -$SO_2NR_2R_3$; -R_2OR_3; -R_2SR_3; -$OCOR_2$; -$OCONR_2R_3$; -NR_2COR_3; -$NR_2CO_2R_3$; -CN; -NO_2; -$C(NR_2)NR_3$; -$CO_2R_2R_3$; -$CONR_2R_3$; -$C(O)R_2$; -$CH(OR_2)R_3$; -$CH_2(OR_2)$; -A-$(CH_2)_m$-NR_2R_3; NR_2R_3; aryl; aralkyl; heteroaryl; and heteroaralkyl; and

Ar_1, Ar_2, and the substituent G are optionally further substituted with one or more substituents selected independently from the group consisting of R_2 and R_4.

In another aspect of the invention, antagonists of Formula II are provided.



II

wherein

---- represents a double or single bond;

X_2 is selected from N and C, and Y_2 is selected from the group consisting of: N; O; S; and CR_5, and at least one of X_2 and Y_2 is a heteroatom;

wherein

R_5 is selected from the group consisting of: H; alkyl; $-CF_3$; $-OR_6$; $-SR_6$; NR_6R_7; $=O$; $=S$; $-=NR_6$; and $=CR_6R_7$; and

wherein

R_6 and R_7 may be independently selected from the group consisting of: H; alkyl; haloalkyl; alkyloxy; alkylamine; cycloalkyl; heterocycloalkyl; aryl; heteroaryl; alkylaryl; alkylheteroaryl; haloaryl; alkyloxyaryl; alkenylaryl; alkenyloxyaryl; and haloheteroaryl; and

Ar_3 and Ar_4 are independently selected from the group consisting of aryl and heteroaryl and one, or both, of Ar_3 and Ar_4 is optionally substituted with one or more substituents G_2;

wherein

G_2 is selected from the group consisting of: haloalkyl; heteroaryl; cycloalkene; alkenyl; alkynyl; A-alkenyl; A-alkynyl; alkyloxy; A-alkyloxy; $-R_6OR_7$; $-R_6OC(O)R_7$; $(CH_2)_m-NR_6R_7$; $-OCH_2CH(Cl)CH_2Cl$; and substituted aryl wherein the aryl substituent is R_8; and

wherein

A is a linker selected from the group consisting of: CH_2; O; NH; S; SO; SO_2; NSO_2; OSO_2; and $-C(NR_6)NR_7$;

m is selected from 0 and 1; and

R_8 is selected from the group consisting of: halo; $-OR_6$; $-SR_6$; $-SOR_6$; $-SO_2R_6$; $-SO_2NR_6R_7$; $-R_6OR_7$ R_6SR_7; $-OCOR_6$; $-OCONR_6R_7$; $-NR_6COR_7$; $-NR_6CO_2R_7$; $-CN$; $-NO_2$; $-C(NR_6)NR_7$; $-CO_2R_6R_7$; $-CONR_6R_7$; $-C(O)R_6$; $-CH(OR_6)R_7$; $-CH_2(OR_6)$; $-A-(CH_2)_m-NR_6R_7$; NR_6R_7; aryl; aralkyl; heteroaryl; and heteroaralkyl; and

Ar_3, Ar_4, and the substituent G_2 are optionally further substituted with one or more substituents selected independently from the group consisting of: R_6 and R_8.

Another aspect of the invention is to provide processes for making the compounds of the present invention.

A further aspect of the invention is to provide a method of inhibiting activation of an mGluR Group I receptor, specifically mGluR5, comprising treating a cell containing said mGluR Group I receptor with an effective amount of a compound of the present invention.

Yet another aspect of the invention is to provide a method of inhibiting neuronal damage caused by excitatory activation of an mGluR Group I receptor, in particular mGluR5, comprising treating neurons with an effective amount of a compound of the present invention.

A further aspect of the invention is to provide a method of treating a disease associated with Group I mGluR activation or amenable to therapeutic intervention with a mGluR Group I antagonist, for example, a disease associated with glutamate-induced neuronal damage, which method comprises the step of administering to a patient, in need of such treatment, for example, a patient suffering from said disease, or at risk of suffering from said disease, a therapeutically effective non-toxic amount of a compound of the present invention. In a particular aspect of the invention a therapeutically effective amount of the present invention would be an amount which selectively antagonizes an mGluR Group I receptor, in particular the mGluR5 receptor.

Other aspects, features and advantages of the present invention will become apparent from the following detailed description. It should be understood, however, that the detailed description and the specific examples, while indicating preferred embodiments of the invention, are given by way of illustration only, since various changes and modifications within the spirit and scope of the invention will become apparent to those skilled in the art from this detailed description.

DEFINITIONS

The term "alkyl" as used herein refers to straight- and branched-chain alkyl radicals containing from 1, 2, 3, 4, 5, or 6 carbon atoms and includes methyl, ethyl and the like.

The term "aryl" as used herein refers to a monocyclic aromatic group such as phenyl and the like or a benzo-fused aromatic group such as indanyl, naphthyl, fluorenyl and the like.

The term "heteroaryl" refers to aromatic compounds containing one or more hetero atoms such as pyridyl, furyl, thienyl and the like or a benzofused aromatic containing one or more heteroatoms such as indolyl, quinolinyl and the like.

The term "heteroatom" as used herein refers to non-carbon atoms such as N, O, S and the like.

The term "cycloalkyl" as used herein refers to a carbocyclic ring containing of 3, 4, 5, 6, 7, or 8 carbons and includes cyclopropyl, cyclohexyl and the like.

The term "heterocycloalkyl" as used herein refers to 3, 4, 5, 6, 7, or 8 membered rings containing 1, 2, or 3 heteroatoms selected from the group consisting of N, S, and O and includes piperidine, piperizine, pyran and the like.

The term "halo" as used herein refers to the halogen radicals fluoro, chloro, bromo, and iodo.

The term "haloalkyl" as used herein refers to an alkyl substituted with one or more halogens, such as bromoethyl, chloromethyl, trichloromethyl and the like.

The term "alkoxy" as used herein refers to a straight- or branched-chain alkoxy containing 1, 2, 3, 4, 5 or 6 carbon atoms and includes methoxy, ethoxy and the like.

The term "alkyloxy" as used herein refers to an alkyl substituted with a hydroxy group such as hydroxyethyl, hydroxypropyl and the like.

The term "alkenyl" as used herein refers to a straight or branched-chain alkyl containing one or more double bonds such as propenyl, vinyl and the like.

The term "aralkyl" as used herein refers to an alkyl substituted with an aryl such as benzyl, phenethyl and the like.

The term "alkylamine" as used herein refers to an alkyl substituted with an amine such as aminomethyl, or dimethylaminoethyl and the like.

The term "alkylaryl" as used herein refers to an aryl substituted with an alkyl group such as methylphenyl, isopropylnaphthyl and the like.

The term "alkylheteroaryl" as used herein refers to a heteroaryl substituted with an alkyl group. Particular examples include methylpyridine, ethylfuran,and the like.

The term "alkynyl" as used herein refers to a straight or branched-chain alkyl containing one or more double bonds such as ethynyl, propynyl, vinyl and the like.

The term "haloaryl" as used herein refers to an aryl substituted with a halogen such as bromophenyl, chlorophenyl and the like.

The term "alkyloxyaryl" as used herein refers to an aryl substituted with an alkyloxy group such as hydroxyethylphenyl and the like.

The term "alkenyloxyaryl" as used herein refers to an aryl susbtituted with an alkenyloxy group such as propenyloxy phenyl and the like.

The term "haloheteroaryl" as used herein refers to a heteroaryl substituted with a halogen. A particular example is 4-chloropyridine.

The term "cycloalkene" as used herein refers to a 3, 4, 5, 6, 7, or 8-member ring, which contains one or more double bonds, and may contain a heteroatom. Particular examples include cyclohexene, tetrahydropyridine and the like.

The term "alkenylaryl" as used herein refers to an aryl substituted with an alkenyl group. A particular example is vinyl benzene.

DETAILED DESCRIPTION OF THE INVENTION

The present invention provides compounds that are potent and selective antagonists of mGluR5. The compounds contemplated by the invention can be represented by the general formula:

$$Ar_1\text{-}L\text{-}Ar_2$$

where Ar^1 is an optionally substituted heterocyclic moiety and Ar^2 is an optionally substituted carbocyclic moiety. The G moiety is a group that not only covalently binds to the Ar^1 and Ar^2 moieties and facilitates adoption of the correct spatial orientation of Ar^1 and Ar^2, but may itself interact with the protein to allow receptor binding.

The Ar^1 moiety is generally defined as a heterocyclic moiety, and the Ar^2 moiety is generally defined as a carbocylic moiety. Ar^1 and Ar^2 can be monocyclic or fused bicyclic groups. Ar^2 is preferably defined as an aryl or alkaryl moiety. Ar^1 is preferably defined as a heterocyclic, heteroaryl or heteroarylalkyl moiety. The ring systems encompassed by Ar^1 can contain up to four heteroatoms, independently selected from the group consisting of N, S, and O. When Ar^1 is a heteroaryl ring or ring system, it preferably contains one or two heteroatoms. At least one of the heteroatoms preferably is nitrogen (N). The heterocyclic or fused heterocylic moiety preferably is selected from the group consisting of quinolyl, quinazolyl, quinoxalyl, 2-pyrimidyl, 4-pyrimidyl, 5-pyrimidyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, and pyrazyl.

Monocyclic Ar^1 groups include, but are not limited to: thiazoyl, furyl, pyranyl, 2H-pyrrolyl, thienyl, pyrroyl, imidazoyl, pyrazoyl, pyridyl, pyrazinyl, pyrimidinyl, and pyridazinyl moieties. Monocyclic Ar^2 group include but are not limited to phenyl

and benzyl. Fused bicyclic Ar^2 include, but are not limited to, naphthyl, fluorenyl, anthrenyl, indenyl, phenanthrenyl, and benzonaphthenyl. Fused bicyclic Ar^1 groups include, but are not limited to: benzothiazole, benzimidazole, 3H-indolyl, indolyl, indazoyl, purinyl, quinolizinyl, isoquinolyl, quinolyl, phthalizinyl, naphthyridinyl, quinazolinyl, cinnolinyl, isothiazolyl, quinoxalinyl indolizinyl, isoindolyl, benzothienyl, benzofuranyl, isobenzofuranyl, and chromenyl moieties. Ar^1 preferably is a 2-pyridyl moiety. Ar^2 preferably is a substituted phenyl moiety.

The Ar^1 and Ar^2 moieties optionally may independently be substituted with one or more moieties selected from the group consisting of halogen, C_1-C_3 alkyl, C_1-C_3 O-alkyl, -OH, $-OCF_3$, -COOR, -COR, -SOR, $-SO_2NRR'$, -NRR', -CN, $-CF_3$, -CO-NRR', -A-$(CH_2)_n$-NRR', wherein A is C, O, N, SO, SO_2, and R and R' are independently selected from the group consisting of C_1-C_3 alkyl, H , cycloalkyl, heterocycloalkyl, aryl, and *n* is 1, 2, 3, or 4.

The L moiety is generally made up of 1-14 atoms. L can be independently selected from the group of atoms: C, H, N, O, and S.

The L moiety can thus be made of a non-cyclic moiety. Several examples of these are -NH- (amine), -S- (thioether), -O- (ether), -CO- (ketone), -CONH- (amide), -$CONHCH_2$-, -CH_2CONH-, -CNHNH- (amidine), -$CNHNHCH_2$-, -C=NO-CH_2- (methoxime), -CH_2NHCH_2-, -CH_2CH_2NH-, -$NHCH_2CO$-, -$NHCH_2CHOH$-, -NHCNHNH.- (guanidine), and -NHCONH- (urea), for example.

The atomic arrangement in the L moiety can also be made to form a five-membered ring. Several examples of these are cyclopentane, cyclopentadiene, furan, thiofuran, pyrrolidine, pyrrole, 2-imidazoline, 3-imidazoline, 4-imidazoline, imidazole, pyrazoline, pyrazolidine, imidazolidine, oxazole, 2-oxazole, thiazole, isoxazole, isothiazole, 1*H*-1,2,4-triazole, 1*H*-1,2,3-triazole, 1,2,4-oxathiazole, 1,3,4-oxathiazole, 1,4,2-dioxazole, 1,4,2-oxathiazole, 1,2,4-oxadiazole, 1,2,4-thiadiazole, 1,2,5-oxadiazole, 1,2,5-thiadiazole, 1,3,4-oxadiazole, 1,3,4-thiadiazole, and 1*H*-tetrazole, for example. The 1,2,4-oxadiazole is most preferred.

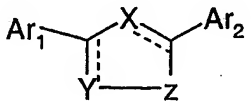
The atomic arrangement in the L moiety can also be made to form a six-membered ring. Several examples of these are cyclohexane, piperidine, tetrahydropyridine, 1,4-dihydropyridine, pyridine, benzene, tetrahydropyran, 3,4-dihydro-2*H*-pyran, 2*H*-pyran, 4*H*-pyran, tetrahydrothiopyran, 3,4-dihydro-2*H*-thiopyran, 2*H*-thiin, 4*H*-thiopyran, morpholine, thiomorpholine, piperazine,

pyridazine, pyrimidine, pyrazine, 1,2,4-triazine, 1,2,3-triazine, 1,3,5-triazine, and 1,2,4,5-tetrazine, for example.

The atomic arrangement in the L moiety can also be made to form a five- or six-membered ring containing one or more carbonyl groups. Several examples of these are 2-azetidinone, 1,2-diazetidin-3-one, cyclopentanone, 2-cyclopentenone, 2-pyrrolidinone, 3-pyrrolin-2-one, succinimide, maleimide, 3-pyrazolidinone, 2-imidazolidone, 4-imidazolin-2-one, 2*H*-imidazol-2-one, 4-imidazolinone, 3-pyrazolin-5-one, hydantoin, 1*H*-imidazole-2,5-dione, 2-oxazoline-4-one, 2-oxazolidinone, 3-oxazolin-5-one, 3(2*H*)-isoxazolone, 2,4-oxazolidinedione, 1,2,4-triazoline-3,5-dione, 2,4-dihydro-3*H*-1,2,4-triazol-3-one, 2*H*-pyran-2-one, 2(1*H*)-pyridone, 2(1*H*)-pyrazinone, 4(3*H*)-pyrimidone, 3,4-dihydropyrimidin-4-one, glutarimide, 4,6-(1*H*,5*H*)-pyrimidinedione, 1,3,5-triazin-2(1*H*)-one, and cyanuric acid, for example.

In a preferred embodiment, L comprises a heterocyclic 5-membered ring system. Preferably, L is an oxazole or an 1,2,4-oxadiazole ring. The L moiety may have either one of two possible orientations with respect to the Ar^1 and Ar^2 groups. Thus, for example, the invention prefers compounds having the configuration 4-(Ar^1)-2-(Ar^2)-oxazole or 3-(Ar^1)– 5-(Ar^2)-1,2,4-oxadiazole.

According to one aspect of the invention, compounds of Formula I are provided.



I

Formula I contains a five member ring containing three variables X, Y, and Z. There are attached to this five member ring two substituents, Ar_1 and Ar_2. The five member ring may contain 0, 1 or 2 double bonds as denoted by the dotted lines in Formula 1. In a preferred embodiment of the invention, the five member ring has 2 double bonds.

In embodiments of the invention, variables X, Y, and Z are independently selected from N, O, S, and substituted carbon, designated CR_1, wherein R_1 is as defined above. At least one of X, Y, or Z must be a heteroatom. In a preferred embodiment of the invention more than one of X, Y, and Z are heteroatoms. In one aspect of the invention two of X, Y, and Z are heteroatoms. While in another aspect of the invention all three of X, Y, and Z are heteroatoms. In a preferred

embodiment of the invention at least one of X, Y, and Z, is N. In a more preferred embodiment of the invention two of X, Y and Z are N. In a further preferred embodiment of the invention, X is N, Y is N and Z is O.

According to a further aspect of the invention the groups Ar_1 and Ar_2 are independently selected from aryl and heteroaryl. Particular embodiments of the invention include those wherein Ar_1 and Ar_2 are independently selected from 5- and 6-member aryl and heteroaryl rings. In more particular embodiments of the invention Ar_1 and Ar_2 are selected from 6-member aryl and heteroaryl rings. Still more particular embodiments of the invention include those where Ar_1 and Ar_2 are independently selected from phenyl, pyridyl, furanyl, thienyl, pyrazinyl, pyrimidinyl, pyridazinyl, pyrrolyl, pyrazolyl, imidazolyl, triazolyl, thiazolyl. In a preferred embodiment of the invention, Ar_1 is selected from phenyl and pyridyl. In a more preferred embodiment of the invention, Ar_1 is selected from pyridyl. In an even more preferred embodiment, Ar_1 is selected from 2-pyridyl. In another preferred embodiment, Ar_2 is selected from phenyl and pyridyl. In a suitable embodiment, Ar_2 is phenyl. In another suitable embodiment, Ar_2 is 3-pyridyl.

According to another aspect of the invention at least one of Ar_1 and Ar_2 is substituted with at least one substituent G. In preferred embodiments of the invention, Ar_2 is substituted with G. Suitable embodiments of the invention include those where G is selected from the group consisting of: haloalkyl; heteroaryl; cycloalkene; alkenyl; alkynyl; A-alkenyl; A-alkynyl; alkyloxy; A-alkyloxy; R_2OR_3; -$R_2OC(O)R_3$; $(CH_2)_m$-NR_2R_3; -$OCH_2CH(Cl)CH_2Cl$; and substituted aryl, wherein R_2 and R_3 are as defined above.

In one embodiment of the invention, G is haloalkyl.

In another embodiment of the invention, G is heteroaryl wherein heteroaryl is selected from the group consisting of: pyridyl; furanyl; thienyl; pyrazinyl; pyrimidinyl; pyridazinyl; pyrrolyl; pyrazolyl; imidazolyl; triazolyl; and thiazolyl. In a preferred embodiment of the invention, G is selected from the group consisting of: pyridyl; furanyl; thienyl; and pyrimidinyl. In a more preferred embodiment of the invention, G is selected from the group consisting of: 2-pyridyl; 3-pyridyl; 4-pyridyl; 3-thienyl; 5-pyrimidinyl; and 3-furanyl.

In yet another preferred embodiment of the invention, G is cycloalkene. In a further preferred embodiment of the invention G is selected from 5- and 6- member

carbocyclic and heterocyclic rings containing one or more double bonds. In a still further preferred embodiment of the invention, G is a 6-member herterocyle containing one double bond. In yet a further embodiment, G is 3-(1,2,5,6-tetrahydropyridyl). In a suitable embodiment G, is N-substituted 3-(1,4,5,6-tetrahydropyridyl, for example 3-*N*-benzyl-(1,2,5,6-tetrahydropyridyl).

According to another aspect of the invention, G is alkenyl. In a more particular embodiment of the invention, G is selected from the group consisting of: vinyl; 2-methylvinyl; propenyl; and butenyl.

According to another aspect of the invention, G is alkynyl. In a more particular embodiment of the invention, G is selected from propargyl and butynyl.

According to yet another aspect of the invention, G is selected from the group consisting of: A-alkenyl; and A-alkynyl; wherein an alkenyl, or alkynyl, respectively, is linked to Ar_1 or Ar_2 though A. In particular embodiments of the invention, A is selected from the group consisting of: CH_2; O; NH; S; SO; SO_2; NSO_2; OSO_2; and $-C(NR_2)NR_3$. In a more particular embodiment of the invention, A is selected from O and NH. In a still more particular embodiment of the invention, G is -OHCH2CH=CH2.

In a still further embodiment of the invention, G is selected from the group consisting of: alkyloxy; and A-alkyloxy; wherein alkyloxy is a straight or branched chain alkyl radical substituted with a hydroxy group and A is a linker. In a more particular embodiment of the invention the alkyloxy group is linked to Ar_1 or Ar_2 through A, and A is selected from the group consisting of: CH_2; O; NH; S; SO; SO_2; NSO_2; OSO_2; and $-C(NR_2)NR_3$. In a more particular embodiment of the invention, A is O, and alkyloxy is selected from hydroxymethyl, hydroxyethyl, and hydroxypropyl. In a more particular embodiment G is $-OCH_2CH_2CH_2OH$.

In a further embodiment of the invention, G is R_2OCOR_3. In a particular embodiment of the invention, G is an alkylester, wherein the ester links to Ar_1 or Ar_2 through an alkyl group. In a more particular embodiment of the invention, G is $-CH_2OC(O)H$.

In still a further embodiment of the invention, G is $(CH_2)_m$-NR_2R_3, wherein m is 0 or 1. In a particular embodiment of the invention, G is $(CH_2)_m$-NR_2R_3, and R_2 and R_3 are independently selected from H, alkyl, alkyloxy, alkylamine, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, alkylaryl, alkylheteroaryl, haloaryl, alkyloxyaryl,

alkenylaryl, alkenyloxyaryl, haloheteroaryl. In a more particular embodiment of the invention, R_2 and R_3 are independently selected from H, and alkyl. In a further embodiment of the invention, R_2 and R_3 are independently selected from H and methyl.

According to another aspect of the invention, G is aryl substituted with a substituents R_4. In particular, the aryl group is selected from the group consisting of: phenyl; naphthyl; anthrenyl; and fluorenyl. The substituent R_4 is selected from the group consisting of: halo; $-OR_2$; $-SR_2$; $-SOR_2$; $-SO2R_2$; $-SO2NR_2R_3$; $-R_2OR_3$; R_2SR_3; $-OCOR_2$; $-OCONR_2R_3$; $-NR_2COR_3$; $-NR_2CO2R_3$; $-CN$; $-NO_2$; OH; $-R_2OH$; $-C(NR_2)NR_3$; $-CO2R_2R_3$; $-CONR_2R_3'$; $-C(O)R_2$; $-CH(OR_2)R_3$; $-CH2(OR_2)$; $-A-(CH_2)_m-NR_2R_3$; NR_2R_3; aryl; aralkyl; heteroaryl; and heteroaralkyl. In a preferred embodiment, aryl is phenyl. In a further preferred embodiment, R_4 is selected from the group consisting of halo; NR_2R_3; alkoxy; and CN. In a further preferred embodiment of the invention, R_4 is selected from the group consisting of F; NH_2; methoxy.

According to another aspect of the invention, each of Ar_1, Ar_2, and G is optionally further substituted with one or more substituents selected from R_2 and R_4. In a preferred embodiment of the invention, Ar_1 is further substituted with a substituent selected from the group consisting of: H; alkyl; haloalkyl; alkyloxy; alkylamine; halo; $-OR_2$; $-SR_2$; $-SOR_2$; $-SO_2R_2$; $-SO_2NR_2R_3$; $-R_2OR_3$; R_2SR_3; $-OCOR_2$; $-OCONR_2R_3$; $-NR_2COR_3$; $-NR_2CO_2R_3$; $-CN$; $-NO_2$; $-C(NR_2)NR_3$; $-CO_2R_2R_3$; $-CONR_2R_3$; $-C(O)R_2$; $-CH(OR_2)R_3$; $-CH_2(OR_2)$; $-A-(CH_2)_m-NR_2R_3$; NR_2R_3; aryl; aralkyl; heteroaryl; heteroaralkyl; cycloalkyl; heterocycloalkyl; alkylaryl; alkylheteroaryl; haloaryl; alkyloxyaryl; alkenylaryl; alkenyloxyaryl; and haloheteroaryl. In a further preferred embodiment of the invention, Ar_1 is is further substituted with a substituent selected from the group consisting of: halo and cyano.

In another aspect of the invention wherein Ar_1 is 2-pyridyl, the further substituent is located at the 5-position of Ar_1. In a further embodiment of the invention, Ar_1 is 5-fluoro-2-pyridyl. In yet another embodiment of the invention, Ar_1 is 5-cyano-2-pyridyl.

According to a further aspect of the invention, Ar_2 is further substituted with one or more substituents selected from the group consisting of: H; alkyl; haloalkyl; alkyloxy; alkylamine; halo; $-OR_2$; $-SR_2$; $-SOR_2$; $-SO_2R_2$; $-SO_2NR_2R_3$; $-R_2OR_3$; $-R_2SR_3$; -

$OCOR_2$; $-OCONR_2R_3$; $-NR_2COR_3$; $-NR_2CO_2R_3$; -CN; $-NO_2$; $-C(NR_2)NR_3$; $-CO_2R_2R_3$; $-CONR_2R_3$; $-C(O)R_2$; $-CH(OR_2)R_3$; $-CH_2(OR_2)$; $-A-(CH_2)_m-NR_2R_3$; NR_2R_3; aryl; aralkyl; heteroaryl; heteroaralkyl; cycloalkyl; heterocycloalkyl; alkylaryl; alkylheteroaryl; haloaryl; alkyloxyaryl; alkenylaryl; alkenyloxyaryl; and haloheteroaryl. In a preferred embodiment of the invention, Ar_2 is further substituted with one or more substituents selected from the group consisting of: alkyl; alkoxy; alkyloxy; hydroxy; halo; cyano; and nitro. In a more preferred embodiment of the invention Ar_2, has a further substituent selected from the group consisting of: cyano; fluoro; chloro; bromo; iodo; and methoxy.

In a more preferred embodiment of the invention, Ar_2 is phenyl or 3-pyridyl, and is substituted with the substituent G at the meta position and a further substituent at the other meta position.

In another embodiment of the invention, the substituent G is optionally further substituted with one or more substituents selected from the group consisting of: H; alkyl; haloalkyl; alkyloxy; alkylamine; halo; $-OR_2$; $-SR_2$; $-SOR_2$; $-SO_2R_2$; $-SO_2NR_2R_3$; $-R_2OR_3$ R_2SR_3; $-OCOR_2$; $-OCONR_2R_3$; $-NR_2COR_3$; $-NR_2CO_2R_3$; -CN; $-NO_2$; $-C(NR_2)NR_3$; $-CO_2R_2R_3$; $-CONR_2R_3$; $-C(O)R_2$; $-CH(OR_2)R_3$; $-CH_2(OR_2)$; $-A-(CH_2)_m-NR_2R_3$; NR_2R_3; aryl; aralkyl; heteroaryl; heteroaralkyl; cycloalkyl; heterocycloalkyl; alkylaryl; alkylheteroaryl; haloaryl; alkyloxyaryl; alkenylaryl; alkenyloxyaryl; and haloheteroaryl. In a more preferred embodiment of the invention, G is optionally further substituted with one or more substituents selected from the group consisting of: alkyl; alkoxy; alkenyl; halo; and cyano. In a particular G is $-OCH_2CH2CH_2OH$, and is further substituted with chloro, to give $-OCH_2CH(Cl)CH_2OH$.

In one aspect of the invention, specific compounds of formula I include:

3-(2-pyridyl)-5-(3-methoxyphenyl)-1,2,4-oxadiazole (B1),

3-(2-pyridyl)-5-(3,5-dichlorophenyl)-1,2,4-oxadiazole (B2),

3-(2-pyridyl)-5-(3-chlorophenyl)-1,2,4-oxadiazole (B3),

3-(2-pyridyl)-5-(2-chlorophenyl)-1,2,4-oxadiazole (B5),

3-(2-pyridyl)-5-[3-(trifluoromethyl)phenyl]-1,2,4-oxadiazole (B6),

3-(2-pyridyl)-5-(3-methylphenyl)-1,2,4-oxadiazole (B9),

3-(2-pyridyl)-5-(1-naphthyl)-1,2,4-oxadiazole (B10),

3-(2-pyridyl)-5-[3-(trifluoromethoxy)phenyl]-1,2,4-oxadiazole (B11),

3-(2-pyridyl)-5-(2,3-difluorophenyl)-1,2,4-oxadiazole (B16),
3-(2-pyridyl)-5-(2,5-difluorophenyl)-1,2,4-oxadiazole (B17),
3-(2-pyridyl)-5-(3,5-difluorophenyl)-1,2,4-oxadiazole (B18),
3-(2-pyridyl)-5-(3-cyanophenyl)-1,2,4-oxadiazole (B21),
3-(2-pyridyl)-5-(3,5-dimethoxyphenyl)-1,2,4-oxadiazol (B23),
3-(2-pyridyl)-5-(2,3-dichlorophenyl)-1,2,4-oxadiazole (B25),
3-(2-pyridyl)-5-(3-chloro-5-cyanophenyl)-1,2,4-oxadiazole (B26),
3-(2-pyridyl)-5-(3-fluoro-5-cyanophenyl)-1,2,4-oxadiazole (B27),
3-(2-pyridyl)-5-(3-chloro-5-fluorophenyl)-1,2,4-oxadiazole (B28),
3-(5-chloropyrid-2-yl)-5-(3-cyanophenyl)-1,2,4-oxadiazole (B29)
3-(5-fluoropyrid-2-yl)-5-(3-cyanophenyl)-1,2,4-oxadiazole (B30),
3-(5-fluoropyrid-2-yl)-5-(3-cyano-5-fluorophenyl)-1,2,4-oxadiazole (B31),
3-(3-fluoropyrid-2-yl)-5-(3-cyanophenyl)-1,2,4-oxadiazole (B32),
3-(5-fluoropyrid-2-yl)-5-(3,5-dimethoxyphenyl)-1,2,4-oxadiazole (B33),
3-(5-methoxypyrid-2-yl)-5-(3-cyanophenyl)-1,2,4-oxadiazole (B34),
3-(2-quinolinyl)-5-(3-cyanophenyl)-1,2,4-oxadiazole (B35),
3-(3-chloro-5-trifluoromethylpyrid-2-yl)-5-(3-cyanophenyl)-1,2,4-oxadiazole (B36),
3-(2-pyridyl)-5-(5-chloro-2-methoxyphenyl)-1,2,4-oxadiazole (B37),
3-(2-pyridyl)-5-(2-chloro-5-methylthiophenyl)-1,2,4-oxadiazole (B39),
3-(2-pyridyl)-5-(2-bromo-5-methoxyphenyl)-1,2,4-oxadiazole (B42),
3-(2-pyridyl)-5-(2,5,6-trifluorophenyl)-1,2,4-oxadiazole (B45),
3-(2-pyridyl)-5-(3-nitrophenyl)-1,2,4-oxadiazole (B19),
3-(2-pyridyl)-5-(3-bromophenyl)-1,2,4-oxadiazole (B22), and pharmaceutically acceptable salts thereof.

In a further aspect of the invention, specific compounds of Formula I include:
2-(3,5-dichlorophenyl)-4-(2-pyridyl)-1,3-oxazole,
2-(3-chlorophenyl)-4-(2-pyridyl)-1,3-oxazole (B50),
2-(3-methoxyphenyl)-4-(2-pyridyl)-1,3-oxazole,
2-(2-chlorophenyl)-4-(2-pyridyl)-1,3-oxazole,
2-(3-trifluorophenyl)-4-(2-pyridyl)-1,3-oxazole,
2-(3-methylphenyl)-4-(2-pyridyl)-1,3-oxazole,
2-(1-naphthyl)-4-(2-pyridyl)-1,3-oxazole,
2-(3-trifluoromethoxyphenyl)-4-(2-pyridyl)-1,3-oxazole,

2-(2,3-difluorophenyl)-4-(2-pyridyl)-1,3-oxazole,
2-(2,5-difluorophenyl)-4-(2-pyridyl)-1,3-oxazole,
2-(3,5-difluorophenyl)-4-(2-pyridyl)-1,3-oxazole,
2-(3-cyanophenyl)-4-(2-pyridyl)-1,3-oxazole (B52),
2-(3,5-dimethoxyphenyl)-4-(2-pyridyl)-1,3-oxazole,
2-(2,3-dichlorophenyl)-4-(2-pyridyl)-1,3-oxazole,
2-(3-chloro-5-cyanophenyl)-4-(2-pyridyl)-1,3-oxazole,
2-(3-fluoro-5-cyanophenyl)-4-(2-pyridyl)-1,3-oxazole,
2-(3-chloro-5-fluorophenyl)-4-(2-pyridyl)-1,3-oxazole,
2-(3-cyanophenyl)-4-(5-chloropyrid-2-yl)-1,3-oxazole,
2-(3-cyanophenyl)-4-(5-fluoropyrid-2-yl)-1,3-oxazole,
2-(3-cyano-5-fluorophenyl)-4-(5-fluoropyrid-2-yl)-1,3-oxazole,
2-(3-cyanophenyl)-4-(3-fluoropyrid-2-yl)-1,3-oxazole,
2-(3,5-dimethoxyphenyl)-4-(5-fluoropyrid-2-yl)-1,3-oxazole,
2-(3-cyanophenyl)-4-(5-methoxypyrid-2-yl)-1,3-oxazole,
2-(3-cyanophenyl)-4-(2-quinolinyl)-1,3-oxazole,
2-(3-cyanophenyl)-4-(3-chloro-5-trifluoromethylpyrid-2-yl)-1,3-oxazole,
2-(5-chloro-2-methoxyphenyl)-4-(2-pyridyl)-1,3-oxazole,
2-(2-chloro-5-methylthiophenyl)-4-(2-pyridyl)-1,3-oxazole,
2-(2-bromo-5-methoxyphenyl)-4-(2-pyridyl)-1,3-oxazole,
2-(2,5,6-trifluorophenyl)-4-(2-pyridyl)-1,3-oxazole,
2-[3-chlorophenyl]-4-[pyridin-2-yl]-1,3-oxazole,
2-(2,5,6-trifluorophenyl)-4-(2-pyridyl)-1,3-oxazole,
2-(3-nitrophenyl)-4-(2-pyridyl-1,3-oxazole,
2-(3-bromophenyl)-4-(2-pyridyl)-1,3-oxazole (B51) and pharmaceutically acceptable salts thereof.

In still a further aspect of the invention, the compounds of the formula I include:

3-(2-Pyridyl)-5-(3-allyloxy-5-(methoxycarbonyl)phenyl)-1,2,4-oxadiazole (B77),
3-(2-Pyridyl)-5-(3-*N,N*-dimethylaminophenyl)-1,2,4-oxadiazole (B82),
3-(2-Pyridyl)-5-(3-cyano-5-(4-pyridyl)phenyl)-1,2,4-oxadiazole (B101),
3-(2-Pyridyl)-5-[2-methoxy-5-(4-pyridyl)phenyl]-1,2,4-oxadiazole (B102),
3-(2-pyridyl)-5-[2-fluoro-5-(4-pyridyl)phenyl]-1,2,4-oxadiazole (B103),

3-(2-Pyridyl)-5-(3-fluoro-5-(4-pyridyl)phenyl)-1,2,4-oxadiazole (B104),
3-(2-Pyridyl)-5-(3-fluoro-5-(3-pyridyl)phenyl)-1,2,4-oxadiazole (B105),
3-(2-Pyridyl)-5-[2-fluoro-5-(3-pyridyl)phenyl]-1,2,4-oxadiazole (B106),
3-(2-Pyridyl)-5-[2-methoxy-5-(3-pyridyl)phenyl]-1,2,4-oxadiazole (B107),
3-(2-Pyridyl)-5-(3-cyano-5-(3-pyridyl)phenyl)-1,2,4-oxadiazole (B108),
3-(5-Fluoro-2-pyridyl)-5-(3-fluoro-5-(3-pyridyl)phenyl)-1,2,4-oxadiazole (B109),
3-(2-Pyridyl)-5-[5-(3-pyridyl-pyrid-3-yl)]-]-1,2,4-oxadiazole (B111),
3-(5-Fluoropyrid-2-yl)]-5-[5-(3-pyridyl-pyrid-3-yl)]-]-1,2,4-oxadiazole (B110),
3-(5-Cyanopyrid-2-yl)-5-(3-(pyrid-3-yl)phenyl)-1,2,4-oxadiazole (B112),
3-(5-Cyanopyrid-2-yl)-5-(3-fluoro-5-(pyrid-3-yl)phenyl)-1,2,4-oxadiazole (B113),
3-(2-Pyridyl)-5-(3-cyano-5-(2-pyridyl)phenyl)-1,2,4-oxadiazole (B124),
3-(2-Pyridyl)-5-[2-methoxy-5-(2-pyridyl)phenyl]-1,2,4-oxadiazole (B125),
3-(2-Pyridyl)-5-[2-fluoro-5-(2-pyridyl)phenyl]-1,2,4-oxadiazole (B126),
3-(2-Pyridyl)-5-[(3-(3-fuorophenyl)-5-fluorophenyl)]-1,2,4-oxadiazole (B114),
3-(2-Pyridyl)-5-(3-cyano-5-(3-thiophene)phenyl)-1,2,4-oxadiazole (B115),
3-(2-Pyridyl)-5-[5-(3-thienyl)-pyrid-3-yl]-1,2,4-oxadiazole (B116),
3-(2-Pyridyl)-5-[5-(3-furyl)-pyrid-3-yl]-1,2,4-oxadiazole (B117),
3-(2-Pyridyl)-5-[5-(3-methoxyphenyl)-pyrid-3-yl]-1,2,4-oxadiazole (B119),
3-(2-Pyridyl)-5-(3-cyano-5-(5-pyrimidyl)phenyl)-1,2,4-oxadiazole (B120),
3-(2-Pyridyl)-5-(3-cyano-5-(3-aminophenyl)phenyl)-1,2,4-oxadiazole (B121),
3-(2-Pyridyl)-5-(3-cyano-5-(3-fluorophenyl)phenyl)-1,2,4-oxadiazole (B122),
3-(2-Pyridyl)-5-[5-(5-pyrimidyl)-pyrid-3-yl]-1,2,4-oxadiazole (B123),
3-(2-Pyridyl)-5-(3-aminomethyl-5-cyanophenyl)-1,2,4-oxadiazole (B127),
3-(2-Pyridyl)-5-[5[(2-propenyl)-pyrid-3-yl]-1,2,4-oxadiazole (B128),
3-(2-Pyridyl)-5-(3-cyano-5-vinylphenyl)-1,2,4-oxadiazole (B129),
3-(2-Pyridyl)-5-(3-cyano-5-(2-hydroxyethyl)phenyl)-1,2,4-oxadiazole (B130),
3-(2-Pyridyl)-5-(3-cyano-5-(2,3-dichloropropoxy)phenyl)-1,2,4-oxadiazole (B131),
3-(2-Pyridyl)-5-(3-allyloxy-5-carboxyphenyl)-1,2,4-oxadiazole (B135),
3-(2-Pyridyl)-5-(3-allyloxy-5-cyanophenyl)-1,2,4-oxadiazole (B136),
3-(2-Pyridyl)-5-(5-cyano-3-[3-hydroxypropyn-1-yl]phenyl)-1,2,4-oxadiazole (B142),
3-(2-Pyridyl)-5-(2-N-methylaminophenyl)-1,2,4-oxadiazole (B144), and
3-(2-Pyridyl)-5-[5-(3-*N*-benzyl-1,2,5,6,tetrahydropyridine)-pyrid-3-yl]-1,2,4-oxadiazole (B143), and pharmaceutically acceptable salts thereof.

In yet a further aspect of the invention, the following compounds of Formula I are provided:

3-(5-Methyl-pyrid-2-yl)-5-(3-cyanophenyl)-1,2,4-oxadiazole (B57),

3-(5-Cyano-pyrid-2-yl)-5-(3-cyanophenyl)-1,2,4-oxadiazole (B58),

3-(2-Pyridyl)-5-(5-bromo-2-methoxyphenyl)-1,2,4-oxadiazole (B62),

3-(2-Pyridyl)-5-(5-bromo-2-fluorophenyl)-1,2,4-oxadiazole (B63),

3-(2-Pyridyl)-5-(5-cyano-2-fluorophenyl)-1,2,4-oxadiazole (B64),

3-(2-Pyridyl)-5-(5-bromopyrid-3-yl)-1,2,4-oxadiazole (B65),

3-(2-Pyridyl)-5-(5-chloro-pyrid-3-yl)-1,2,4-oxadiazole (B66),

3-(5-Cyanopyrid-2-yl)-5-(5-bromo-pyrid-3-yl)-1,2,4-oxadiazole (B67),

3-(5-Fluoropyrid-2-yl)-5-(5-bromo-pyrid-3-yl-1,2,4-oxadiazole (B68),

3-(2-Pyridyl)-5-(2-thiomethoxy-pyrid-3-yl)]-1,2,4-oxadiazole (B69),

3-(2-Pyridyl)-5-(5-methylpyrid-3-yl)-1,2,4-oxadiazole (B70),

3-(2-Pyridyl)-5-(5-methoxypyrid-3-yl)-1,2,4-oxadiazole (B72),

3-(2-Pyridyl)-5-(3-cyano-5-methylphenyl)-1,2,4-oxadiazole (B73),

3-(2-Pyridyl)-5-(3-fluoro-5-bromophenyl)-1,2,4-oxadiazole (B74),

3-(2-Pyridyl)-5-(3-iodo-5-bromophenyl)-1,2,4-oxadiazole (B75),

3-(5-Fluoro-2-pyridyl)-5-(3-fluoro-5-bromophenyl)-1,2,4-oxadiazole (B76),

3-(2-Pyridyl)-5-(3-iodo-5-(methylphenylester)-1,2,4-oxadiazole (B78),

3-(2-Pyridyl)-5-(3-methoxy-5-(methoxycarbonyl)phenyl)-1,2,4-oxadiazole (B79),

3-(2-Pyridyl)-5-(3-bromo-5-cyanophenyl)-1,2,4-oxadiazole (B80),

3-(2-Pyridyl)-5-(5-cyano-3-iodophenyl)-1,2,4-oxadiazole (B81),

3-(5-Cyano-2-pyridyl)-5-(3-bromophenyl)-1,2,4-oxadiazole (B59),

3-(5-Cyano-2-pyridyl)-5-(3-cyano-5-fluorophenyl)-1,2,4-oxadiazole (B60),

3-(5-Cyano-2-pyridyl)-5-(3-bromo-5-fluorophenyl)-1,2,4-oxadiazole (B61),

3-(2-Pyridyl)-5-(5-cyano-2-methoxyphenyl)-1,2,4-oxadiazole (B97),

3-(2-Pyridyl)-5-(2-cyano-5-methoxyphenyl)-1,2,4-oxadiazole (B98),

3-(2-Pyridyl)-5-(5-cyano-pyrid-3-yl)-1,2,4-oxadiazole (B99),

3-(2-Pyridyl)-5-(3-cyano-5-(methoxycarbonyl)phenyl)-1,2,4-oxadiazole (B100),

3-(2-Pyridyl)-5-(5-phenyl-pyrid-3-yl)-1,2,4-oxadiazole (B118),

3-(2-Pyridyl)-5-(3-cyano-5-methoxyphenyl)-1,2,4-oxadiazole (B134),

3-(2-Pyridyl)-5-(3-cyano-5-hydroxyphenyl)-1,2,4-oxadiazole (B137),

3-(2-Pyridyl)-5-(3-cyano-5-propoxyphenyl)-1,2,4-oxadiazole (B141),

2-(3-Cyanophenyl)-4-(pyridin-2-yl)-1,3-thiazole (B146),

2-(3-Bromo-5-iodophenyl)-4-pyridin-2-yl)-1,3-oxazole (B147),

2-(2-Pyridyl)-5-(3-iodophenyl)-1,3,4-oxadiazole (B148),

2-(2-Pyridyl)-5-(3-cyanophenyl)-1,3,4-oxadiazole (B149),

2-(2-Pyridyl)-5-(3-cyanophenyl)-1,3,4-triazole (B150),

3-(5-Chloropyrid-2-yl)-5-(3-cyano-5-fluorophenyl)-1,2,4-oxadiazole (B83),

3-(5-Chloropyrid-2-yl)-5-(3-cyano-5-chlorophenyl)-1,2,4-oxadiazole (B84),

3-(5-Chloropyrid-2-yl)-5-(3-chloro-5-fluorophenyl)-1,2,4-oxadiazole (B85),

3-(5-Chloropyrid-2-yl)-5-(3-cyano-5-methoxyphenyl)-1,2,4-oxadiazole (B86),

3-(5-Fluoropyrid-2-yl)-5-(3-cyano-5-chlorophenyl)-1,2,4-oxadiazole (B87),

3-(5-Fluoropyrid-2-yl)-5-(3-fluoro-5-chlorophenyl)-1,2,4-oxadiazole (B88),

3-(5-Fluoropyrid-2-yl)-5-(3-cyano-5-methoxyphenyl)-1,2,4-oxadiazole (B89),

3-(5-Cyanopyrid-2-yl)-5-(3-cyano-5-chlorophenyl)-1,2,4-oxadiazole (B90),

3-(5-Cyanopyrid-2-yl)-5-(3-fluoro-5-chlorophenyl)-1,2,4-oxadiazole (B91)

3-(5-Cyanopyrid-2-yl)-5-(3-cyano-5-methoxyphenyl)-1,2,4-oxadiazole (B92),

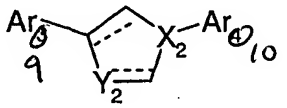
3-(5-Fluoropyrid-2-yl)-5-(3,5-di-cyanophenyl)-1,2,4-oxadiazole (B93),

3-(3-(4-Dimethylaminobutoxy)-pyrid-2-yl)-5-(3-cyano-5-fluorophenyl)-1,2,4-oxadiazole (B94),

3-(3-(5-Dimethylaminopentyloxy)-pyrid-2-yl)-5-(3-Cyano-5-fluorophenyl)-1,2,4-oxadiazole (B95), and

[3-(3-(6-Dimethylaminohexyloxy)-pyrid-2-yl)-5-(3-cyano-5-fluorophenyl)-1,2,4-oxadiazole (B96).

The present invention also provides compounds that are potent and selective antagonists of mGluR5, which may be represented by Formula II.



According to another aspect of the invention there is a five member ring containing two variables X_2, and Y_2. There are attached to this five member ring two substituents, Ar9 and Ar10. The five member ring may contain 0, 1, or 2 double bonds as denoted by the dotted lines in Formula II. In a preferred embodiment of the invention, the five member ring has two double bonds.

In embodiments of the invention, the variable X_2 is selected from the group consisting of: N and C, and the variable Y_2 is selected from the group consisting of: N; O; S; and CR_5, wherein at least one of X_2, and Y_2 must be a heteroatom. In the case where Y_2 is CR_5, R_5 is selected from the group consisting of: H; alkyl; $-CF_3$; $-OR_6$; $-SR_6$; NR_6R_7; -C(O); -C(S); $-C=NR_6$; and $=CR_6R_7$, wherein R_6 and R_7 may be independently selected from the group consisting of: H; alkyl; haloalkyl; alkyloxy; alkylamine; cycloalkyl; heterocycloalkyl; aryl; heteroaryl; alkylaryl; alkylheteroaryl; haloaryl; alkyloxyaryl; alkenylaryl; alkenyloxyaryl; and haloheteroaryl. In preferred embodiments of the invention, both X_2 and Y_2 are heteroatoms. In a further preferred embodiment of the invention, X_2 is N. In a still more preferred embodiment of the invention Y_2 is N. In a more preferred embodiment of the invention, X_2 and Y_2 are both N.

According to another aspect of the invention, the group Ar_3 and Ar_4, are independently selected from the group consisting of aryl and heteroaryl. Particular embodiments of the invention include those wherein Ar_3 and Ar_4 are independently selected from 5- and 6-member aryl and heteroaryl rings. In more particular embodiments of the invention, Ar_3 and Ar_4 are selected from 6-member aryl and heteroaryl rings. Still more particular embodiments of the invention include those where Ar_3 and Ar_4 are independently selected from phenyl, pyridyl, furanyl, thienyl, pyrazinyl, pyrimidinyl, pyridazinyl, pyrrolyl, pyrazolyl, imidazolyl, triazolyl, and thiazolyl. In a preferred embodiment of the invention, Ar_3 and Ar_4 are independently selected from phenyl and pyridyl. In a more preferred embodiment of the invention, one of Ar_3 and Ar_4 is phenyl and one is pyridyl.

According to still a another embodiment of the invention, Ar_3 and Ar_4 are optionally substituted with one or more substituents G_2, wherein G_2 is selected from the group consisting of: haloalkyl; heteroaryl; cycloalkene; alkenyl; alkynyl; A-alkenyl; A-alkynyl; alkyloxy; A-alkyloxy; $-R_6OR_7$; $-R_6OC(O)R_7$; $(CH_2)_m-NR_6R_7$; $-OCH_2CH(Cl)CH_2Cl$; and substituted aryl wherein the aryl substituent is R_8. In a particular embodiment wherein one, or both, of Ar_3 and Ar_4 are substituted with G_2, G_2 is selected from the group consisting of: A-alkenyl; Alkynyl; and A-alkyloxy, and A is selected from the group consisting of: CH_2; O; NH; S; SO; SO_2; OSO_2; NSO_2; and $-C(NR_6)NR_7$. In a more particular embodiment, G_2 is $(CH_2)_m-NR_6R_7$. In an embodiment of the invention, G_2 is substituted aryl and the substituent R_8 is

selected from the group consisting of: halo; -OR_6; -SR_6; -SOR_6; -SO_2R_6; -$SO_2NR_6R_7$; -R_6OR_7 R_6SR_7; -$OCOR_6$; -$OCONR_6R_7$; -NR_6COR_7; -$NR_6CO_2R_7$; -CN; -NO_2; -$C(NR_6)NR_7$; -$CO_2R_6R_7$; -$CONR_6R_7$; -$C(O)R_6$; -$CH(OR_6)R_7$; -$CH_2(OR_6)$; -A-$(CH_2)_m$-NR_6R_7; NR_6R_7; aryl; aralkyl; heteroaryl; and heteroaralkyl.

In a further embodiment of the invention, each of Ar_3 and Ar_4 and G_2 is further substituted with one or more substituents selected from R_6, and R_8. In a preferred embodiment of the invention, each of Ar_3 and Ar_4 is independently further substituted with one or more substituents selected from the group consisting of: H; alkyl; haloalkyl; alkyloxy; alkylamine; halo; -OR_6; -SR_6; -SOR_6; -SO_2R_6; -$SO_2NR_6R_6$; -R_6OR_7 R_6SR_7; -$OCOR_6$; -$OCONR_6R_7$; -NR_6COR_7; -$NR_6CO_2R_7$; -CN; -NO_2; -$C(NR_6)NR_7$; -$CO_2R_6R_7$; -$CONR_6R_7$; -$C(O)R_6$; -$CH(OR_6)R_7$; -$CH_2(OR_6)$; -A-$(CH_2)_m$-NR_6R_7; NR_6R_7; aryl; aralkyl; heteroaryl; heteroaralkyl; cycloalkyl; heterocycloalkyl; alkylaryl; alkylheteroaryl; haloaryl; alkyloxyaryl; alkenylaryl; alkenyloxyaryl; and haloheteroaryl.

According to a further aspect of the invention, Ar_3 and Ar_4 are independently substituted with a substituent selected from the group consisting of halo and cyano.

In specific embodiments of the invention, the compounds of formula II include:

4-(3-Cyanophenyl)-1-(2-pyridyl)-1H-imidazole (B151)

1-(3-Cyanophenyl)-4-(2-pyridyl)-1H-imidazole (B152).

Testing of compounds for mGluR Group I antagonist activity

The pharmacological properties of the compounds of the invention can be analyzed using standard assays for functional activity. Examples of glutamate receptor assays are well known in the art, for example, see Aramori *et al., Neuron* 8:757 (1992); Tanabe *et* al., *Neuron* 8:169 (1992); Miller *et al., J. Neuroscience* 15: 6103 (1995); Balazs, *et al., J. Neurochemistry* 69:151 (1997). The methodology described in those publications is incorporated herein by reference.

Conveniently, the compounds of the invention can be studied by means of an assay that measures the mobilization of intracellular calcium, $[Ca^{2+}]_i$ in cells expressing mGluR5 that can bind the compounds. A well-known cell line which is suitable for this purpose is described in Miller *et al., J. Neuroscience* 15: 6103

(1995), the contents of which are hereby incorporated by reference. It has been shown that exposure to rat astrocytes to the growth factors, basic fibroblast growth factor, EGF, or transforming growth factor-α markedly increased the protein expression and functional activity of endogenous mGluR5 (Miller *et al., J. Neuroscience, 15(9)*: 6103-6109, 1995).

In brief, primary astrocyte cultures were prepared from 3-5 day old Sprague-Dawley rat pups using a modification of Miller *et al.* were plated on poly-L lysine coated flasks in Dulbecco's modified Eagle's medium (DMEM) containing fetal calf serum (FCS). For cuvette analysis, cultures were up-regulated with growth factors in flasks for 3-5 days, then harvested and prepared for measurement of $[Ca^{2+}]_i$ mobilization as previously described (Nemeth et al., 1998).

For FLIPR analysis, cells were seeded on poly-D lysine coated clear bottom 96-well plates with black sides and analysis of $[Ca^{2+}]_i$ mobilization was performed 3 days following the growth factor up-regulation.

FLIPR experiments were done using a laser setting of 0.800 W and a 0.4 second CCD camera shutter speed. Each FLIPR experiment was initiated with 180 µL of buffer present in each well of the cell plate. After each addition of compound, the fluorescence signal was sampled 50 times at 1 second intervals followed by 3 samples at 5 second intervals. Responses were measured as the peak height of the response within the sample period.

EC_{50} and IC_{50} determinations were made from data obtained from 8 point concentration response curves (CRC) performed in duplicate. Agonist CRC were generated by scaling all responses to the maximal response observed for the plate. Antagonist block of the agonist challenge was normalized to the average response of the agonist challenge in 14 control wells on the same plate. A detailed protocol for testing the compounds of the invention is provided below at Example 6.

Preparation of pharmaceutical compositions containing mGluR antagonists, and their use in treating neurological disorders

The compounds of the present invention may be useful for treating neurological disorders or diseases. While these compounds typically will be used in therapy for human patients, they also can be used in veterinary medicine, to treat similar or identical diseases.

In therapeutic and/or diagnostic applications, the compounds of the invention can be formulated for a variety of modes of administration, including systemic and topical or localized administration. Techniques and formulations generally may be found in REMINGTON'S PHARMACEUTICAL SCIENCES (18th ed.), Mack Publishing Co. (1990).

The compounds according to the invention are effective over a wide dosage range. For example, in the treatment of adult humans, dosages from about 0.01 to about 1000 mg, preferably from about 0.5 to about 100 mg, per day may be used. A most preferable dosage is about 2 mg to about 70 mg per day. The exact dosage will depend upon the route of administration, the form in which the compound is administered, the subject to be treated, the body weight of the subject to be treated, and the preference and experience of the attending physician.

Pharmaceutically acceptable salts are generally well known to those of ordinary skill in the art, and may include, by way of example but not limitation, acetate, benzenesulfonate, besylate, benzoate, bicarbonate, bitartrate, bromide, calcium edetate, camsylate, carbonate, citrate, edetate, edisylate, estolate, esylate, fumarate, gluceptate, gluconate, glutamate, glycollylarsanilate, hexylresorcinate, hydrabamine, hydrobromide, hydrochloride, hydroxynaphthoate, iodide, isethionate, lactate, lactobionate, malate, maleate, mandelate, mesylate, mucate, napsylate, nitrate, pamoate (embonate), pantothenate, phosphate/disphosphate, polygalacturonate, salicylate, stearate, subacetate, succinate, sulfate, tannate, tartrate, or teoclate. Other pharmaceutically acceptable salts may be found, for example, in REMINGTON'S PHARMACEUTICAL SCIENCES (18th ed.), *supra*.

Preferred pharmaceutically acceptable salts include, for example, acetate, benzoate, bromide, carbonate, citrate, gluconate, hydrobromide, hydrochloride, maleate, mesylate, napsylate, pamoate (embonate), phosphate, salicylate, succinate, sulfate, or tartrate.

Depending on the specific conditions being treated, such agents may be formulated into liquid or solid dosage forms and administered systemically or locally. The agents may be delivered, for example, in a timed- or sustained-release form as is known to those skilled in the art. Techniques for formulation and administration may be found in REMINGTON'S PHARMACEUTICAL SCIENCES; (18th ed.),

supra. Suitable routes may include oral, buccal, sublingual, rectal, transdermal, vaginal, transmucosal, nasal or intestinal administration; parenteral delivery, including intramuscular, subcutaneous, intramedullary injections, as well as intrathecal, direct intraventricular, intravenous, intraperitoneal, intranasal, or intraocular injections, *inter alia*.

For injection, the agents of the invention may be formulated in aqueous solutions, preferably in physiologically compatible buffers such as Hank's solution, Ringer's solution, or physiological saline buffer. For such transmucosal administration, penetrants appropriate to the barrier to be permeated are used in the formulation. Such penetrants are generally known in the art.

Use of pharmaceutically acceptable carriers to formulate the compounds herein disclosed for the practice of the invention into dosages suitable for systemic administration is within the scope of the invention. With proper choice of carrier and suitable manufacturing practice, the compositions of the present invention, in particular, those formulated as solutions, may be administered parenterally, such as by intravenous injection. The compounds can be formulated readily using pharmaceutically acceptable carriers well known in the art into dosages suitable for oral administration. Such carriers enable the compounds of the invention to be formulated as tablets, pills, capsules, liquids, gels, syrups, slurries, suspensions and the like, for oral ingestion by a patient to be treated.

Pharmaceutical compositions suitable for use in the present invention include compositions wherein the active ingredients are contained in an effective amount to achieve its intended purpose. Determination of the effective amounts is well within the capability of those skilled in the art, especially in light of the detailed disclosure provided herein.

In addition to the active ingredients, these pharmaceutical compositions may contain suitable pharmaceutically acceptable carriers comprising excipients and auxiliaries which facilitate processing of the active compounds into preparations which can be used pharmaceutically. The preparations formulated for oral administration may be in the form of tablets, dragees, capsules, or solutions.

Pharmaceutical preparations for oral use can be obtained by combining the active compounds with solid excipients, optionally grinding a resulting mixture, and processing the mixture of granules, after adding suitable auxiliaries, if desired, to

obtain tablets or dragee cores. Suitable excipients are, in particular, fillers such as sugars, including lactose, sucrose, mannitol, or sorbitol; cellulose preparations, for example, maize starch, wheat starch, rice starch, potato starch, gelatin, gum tragacanth, methyl cellulose, hydroxypropylmethyl-cellulose, sodium carboxymethyl-cellulose (CMC), and/or polyvinylpyrrolidone (PVP: povidone). If desired, disintegrating agents may be added, such as the cross-linked polyvinylpyrrolidone, agar, or alginic acid or a salt thereof such as sodium alginate.

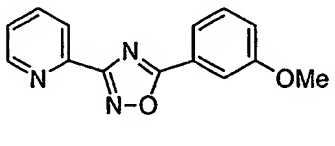
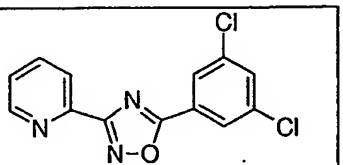
Dragee cores are provided with suitable coatings. For this purpose, concentrated sugar solutions may be used, which may optionally contain gum arabic, talc, polyvinylpyrrolidone, carbopol gel, polyethylene glycol (PEG), and/or titanium dioxide, lacquer solutions, and suitable organic solvents or solvent mixtures. Dye-stuffs or pigments may be added to the tablets or dragee coatings for identification or to characterize different combinations of active compound doses.

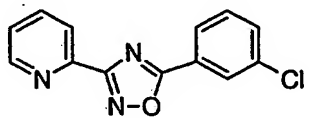
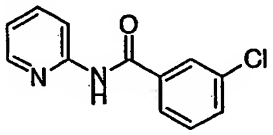
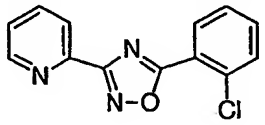
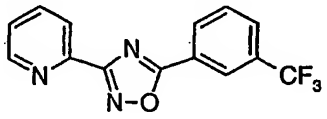
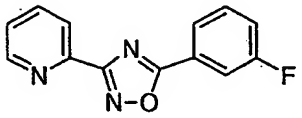
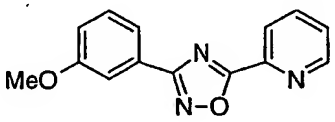
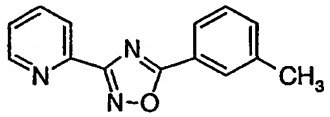
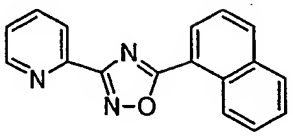
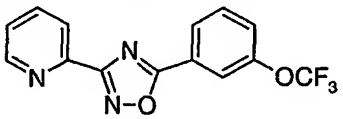
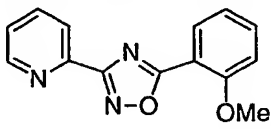
Pharmaceutical preparations which can be used orally include push-fit capsules made of gelatin, as well as soft, sealed capsules made of gelatin, and a plasticizer, such as glycerol or sorbitol. The push-fit capsules can contain the active ingredients in admixture with filler such as lactose, binders such as starches, and/or lubricants such as talc or magnesium stearate and, optionally, stabilizers. In soft capsules, the active compounds may be dissolved or suspended in suitable liquids, such as fatty oils, liquid paraffin, or liquid polyethylene glycols (PEGs). In addition, stabilizers may be added.

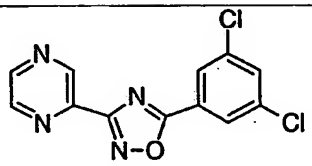
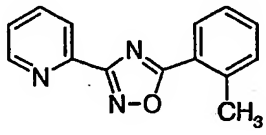
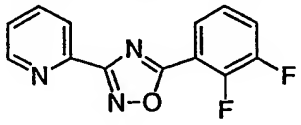
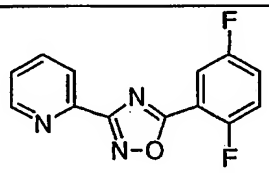
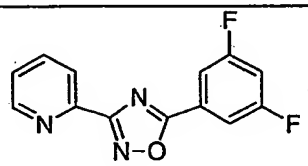
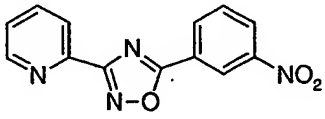
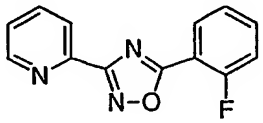
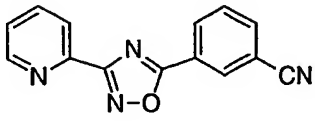
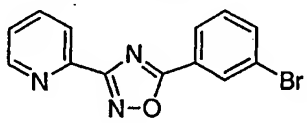
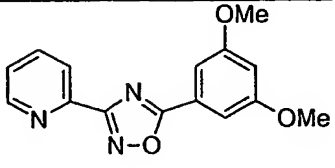
The present invention will be understood more readily by reference to the following examples, which are provided by way of illustration and are not intended to be limiting of the present invention.

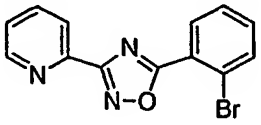
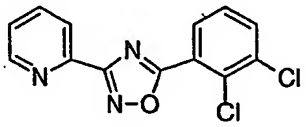
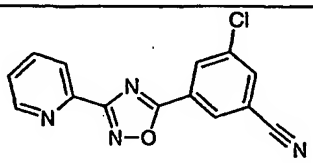
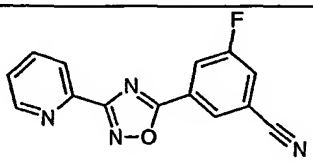
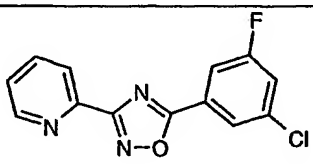
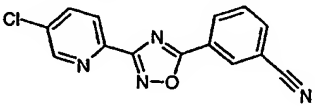
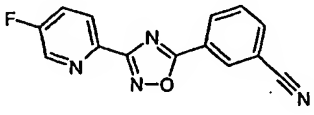
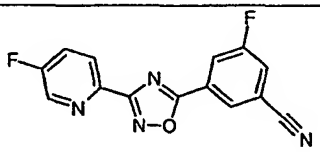
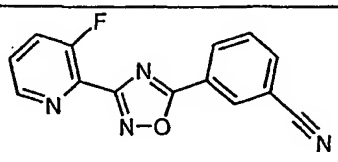
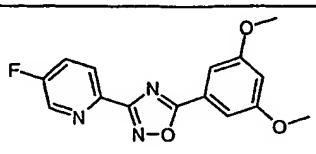
Tables 1, 2, and 3 summarize specific exemplified compounds of the present invention.

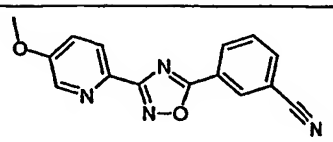
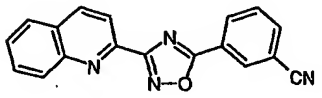
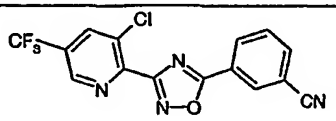
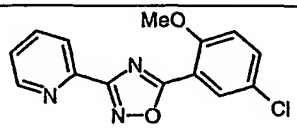
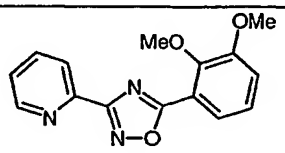
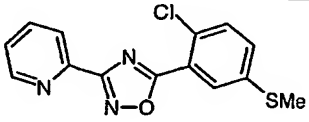
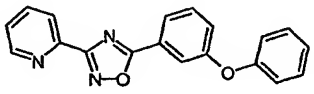
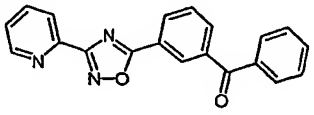
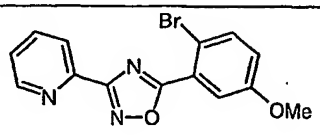
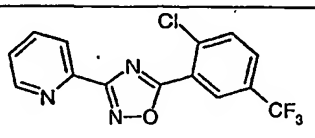
Table 1

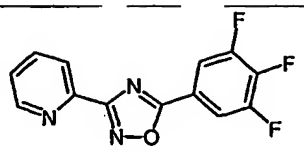
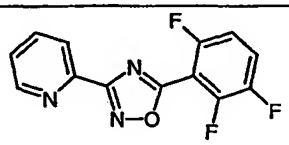
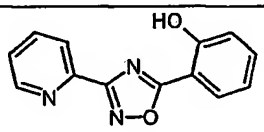
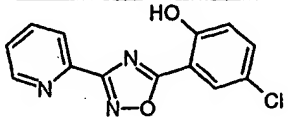
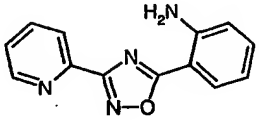
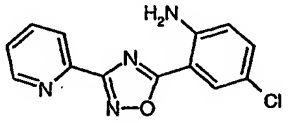
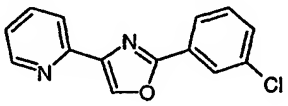
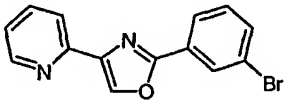
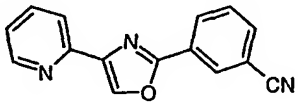
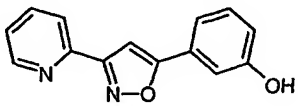
B1	
B2	

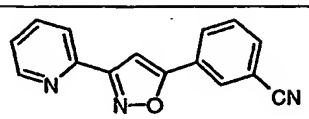
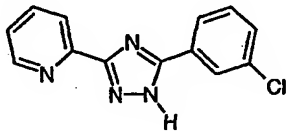
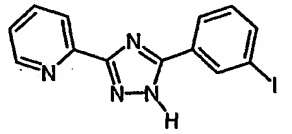
B3	
B4	
B5	
B6	
B7	
B8	
B9	
B10	
B11	
B12	

B13	
B15	
B16	
B17	
B18	
B19	
B20	
B21	
B22	
B23	

B24	
B25	
B26	
B27	
B28	
B29	
B30	
B31	
B32	
B33	

B34	
B35	
B36	
B37	
B38	
B39	
B40	
B41	
B42	
B43	

B44	
B45	
B46	
B47	
B48	
B49	
B50	
B51	
B52	
B53	

B54	
B55	
B56	

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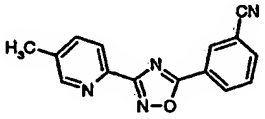
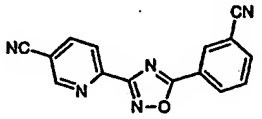
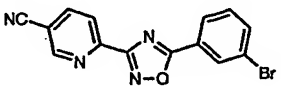
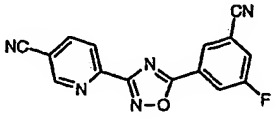
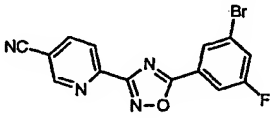
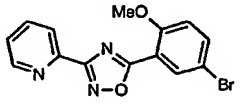
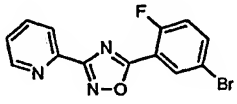
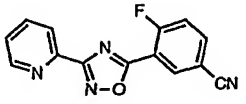
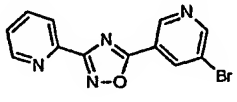
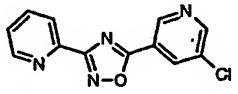
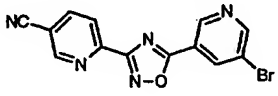
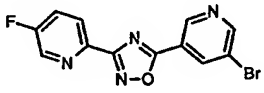
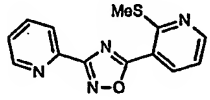
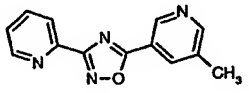
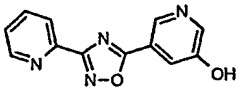
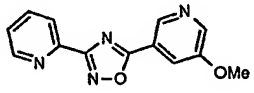
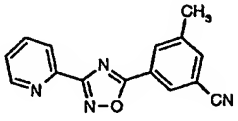
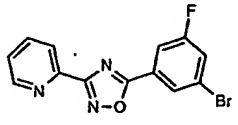
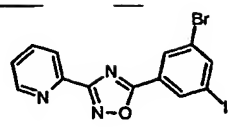
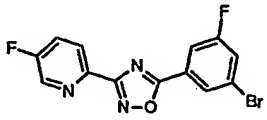
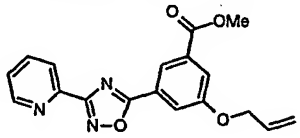
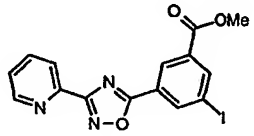
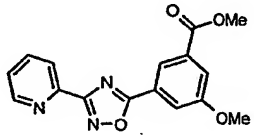
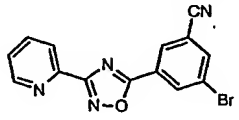
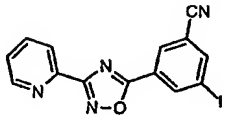
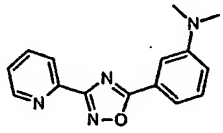
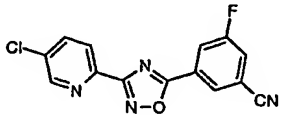
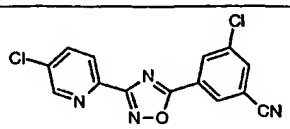
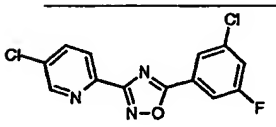
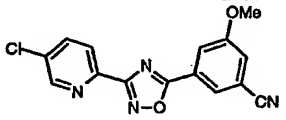
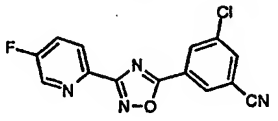
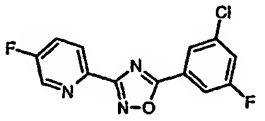
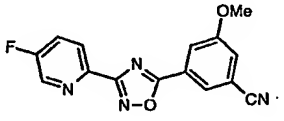
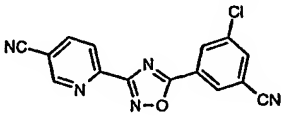
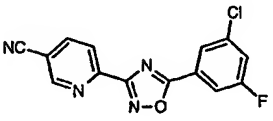
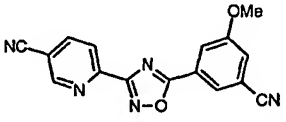
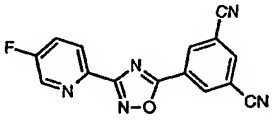
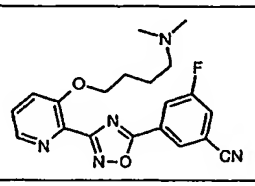
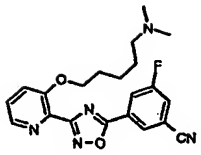
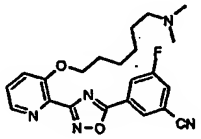
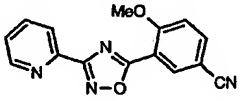
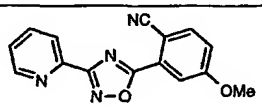
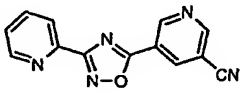
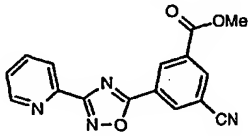
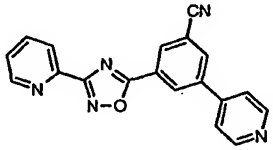
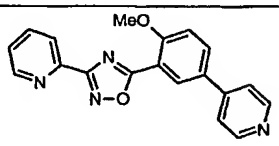
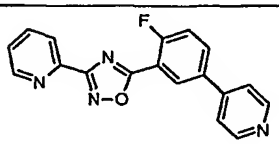
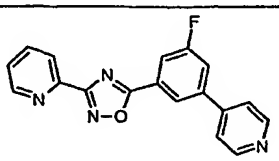
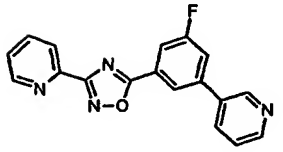
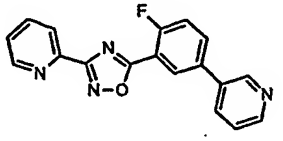
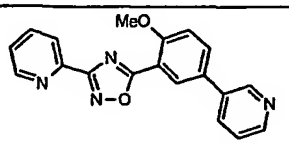
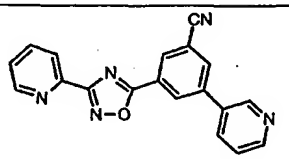
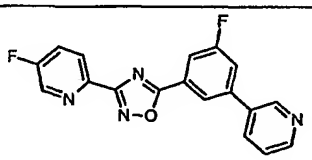
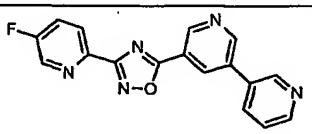
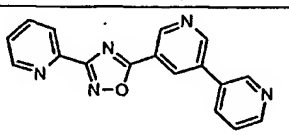
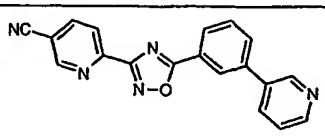
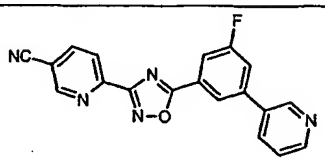
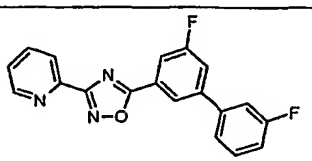
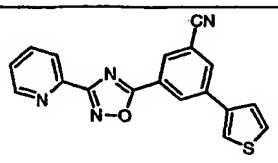
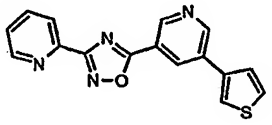
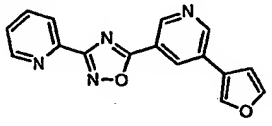
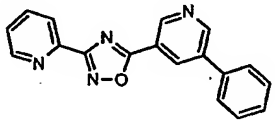
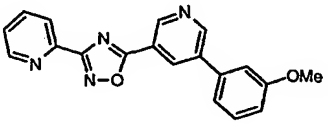
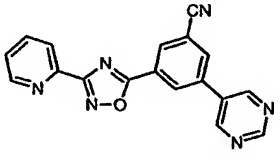
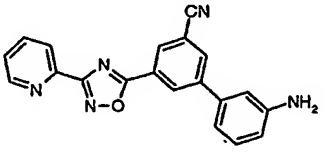
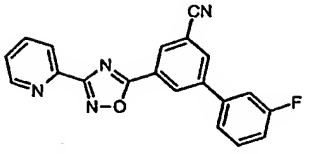
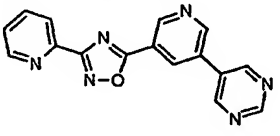
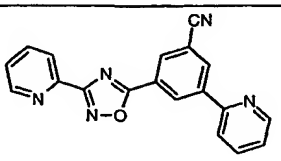
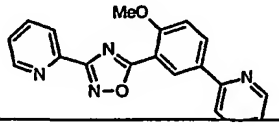
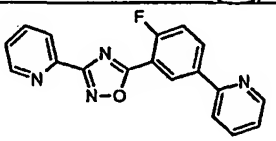
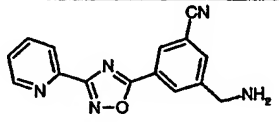
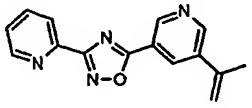
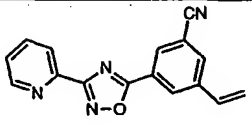
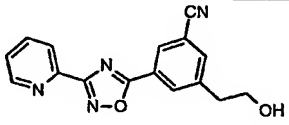
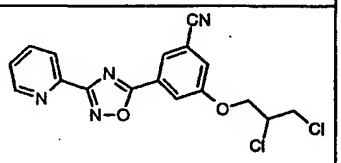
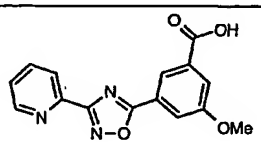
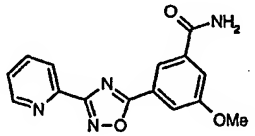
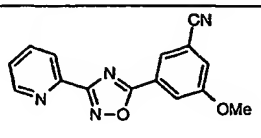
B57	
B58	
B59	
B60	
B61	
B62	
B63	
B64	
B65	
B66	
B67	
B68	
B69	
B70	
B71	
B72	
B73	
B74	

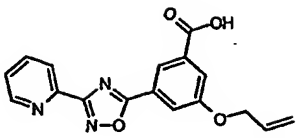
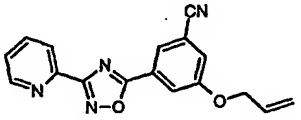
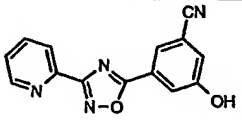
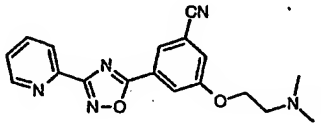
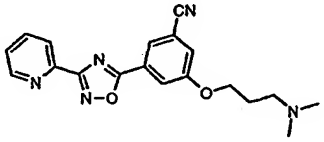
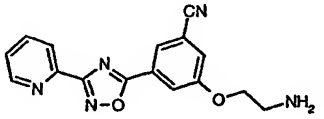
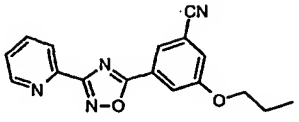
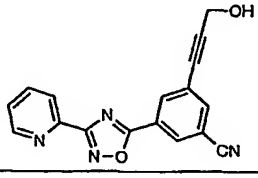
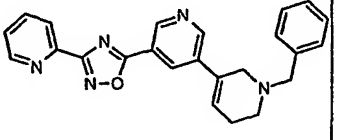
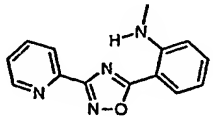
B75	
B76	
B77	
B78	
B79	
B80	
B81	
B82	
B83	
B84	
B85	
B86	
B87	
B88	
B89	
B90	
B91	
B92	
B93	
B94	

B95	
B96	
B97	
B98	
B99	
B100	
B101	
B102	
B103	
B104	

B105	
B106	
B107	
B108	
B109	
B110	
B111	
B112	
B113	
B114	

B115	
B116	
B117	
B118	
B119	
B120	
B121	
B122	
B123	
B124	

B125	
B126	
B127	
B128	
B129	
B130	
B131	
B132	
B133	
B134	

B135	
B136	
B137	
B138	
B139	
B140	
B141	
B142	
B143	
B144	

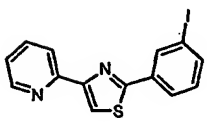
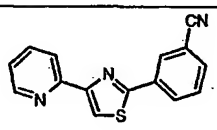
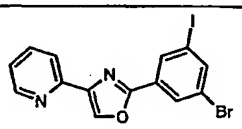
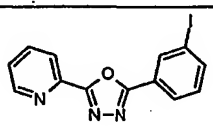
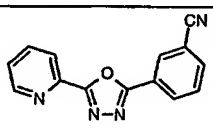
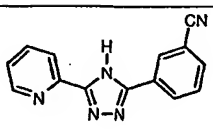
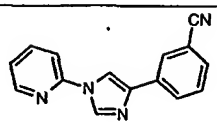
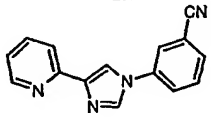
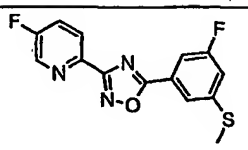
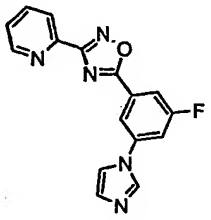
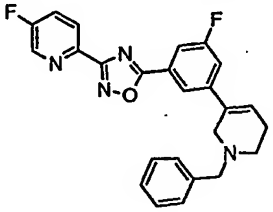
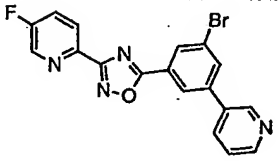
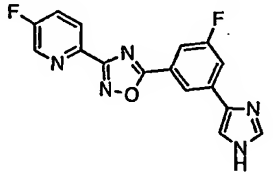
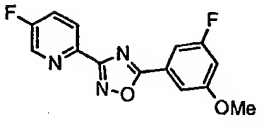
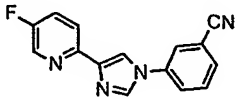
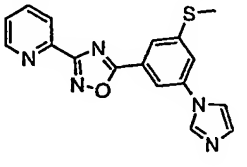
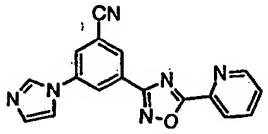
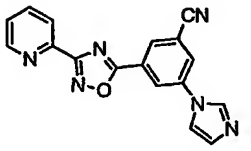
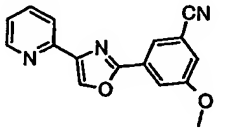
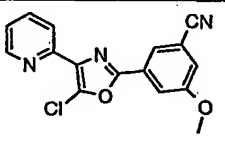
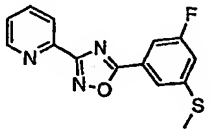
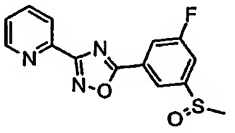
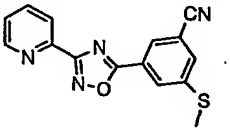
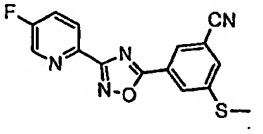
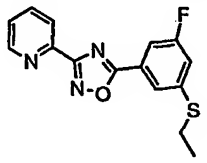
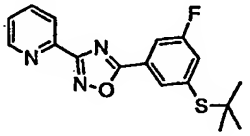
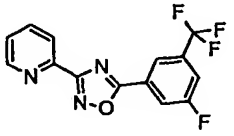
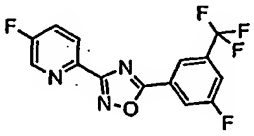
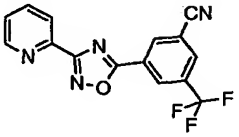
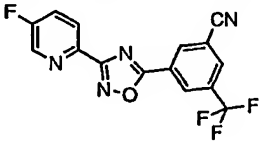
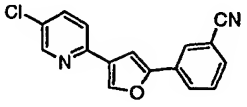
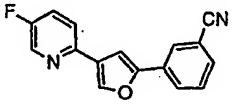
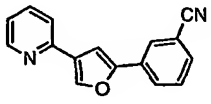
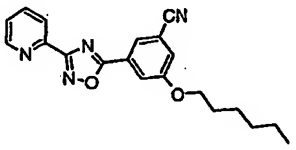
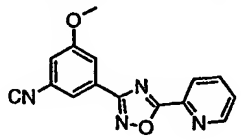
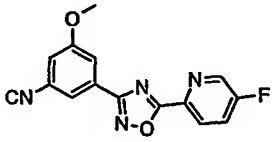
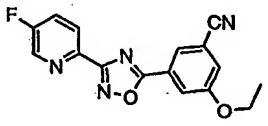
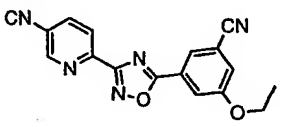
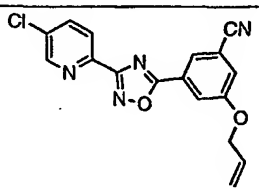
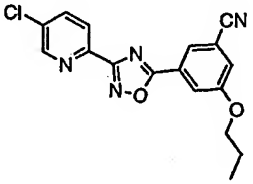
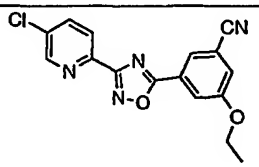
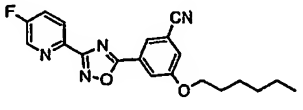
B145	
B146	
B147	
B148	
B149	
B150	
B151	
B152	

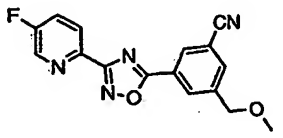
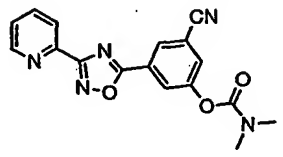
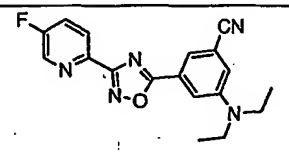
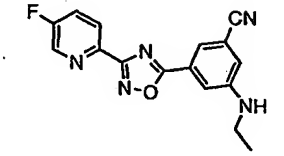
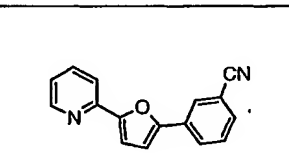
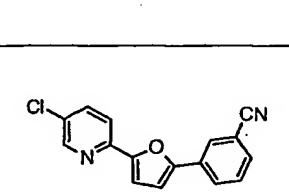
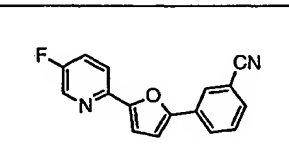
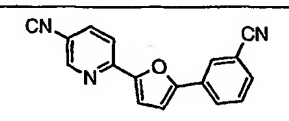
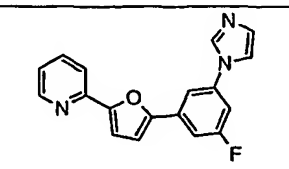
Table 3

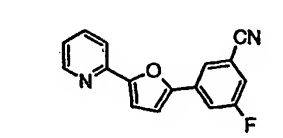
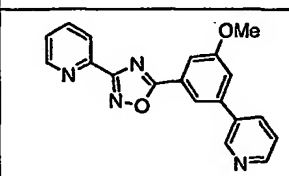
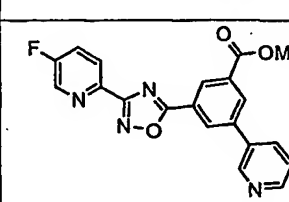
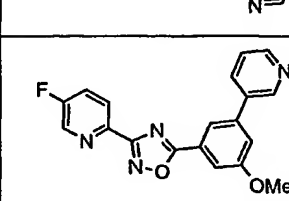
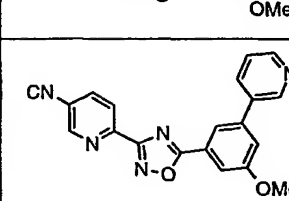
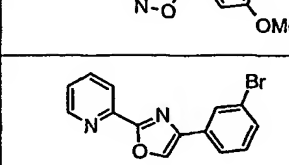
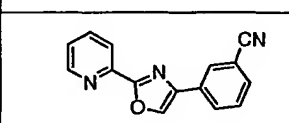
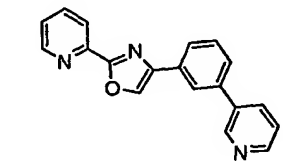
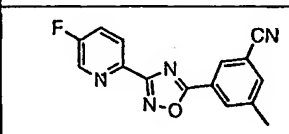
B153	
B154	
B250	
B212	
B251	
B213	
B252	
B253	

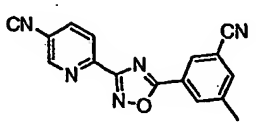
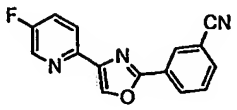
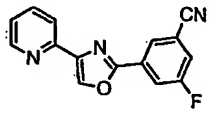
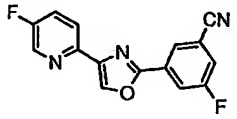
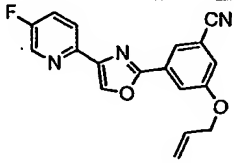
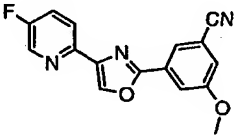
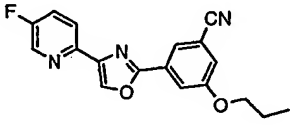
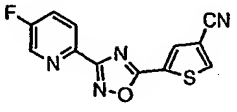
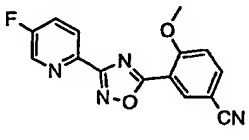
B254	
B255	
B269	
B272	
B216	
B217	
B214	
B215	

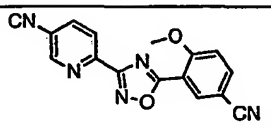
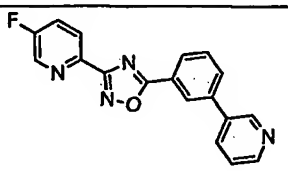
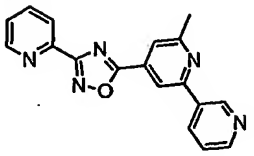
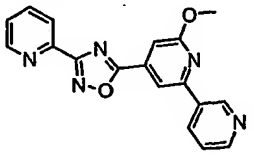
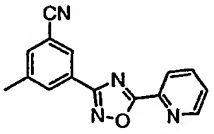
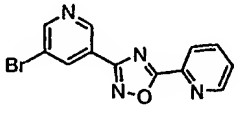
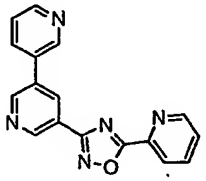
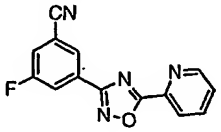
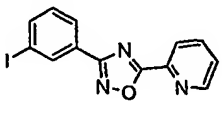
B218	
B219	
B155	
B156	
B223	
B224	
B258	
B257	
B256	

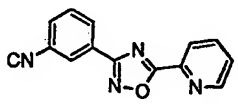
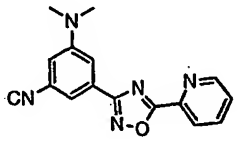
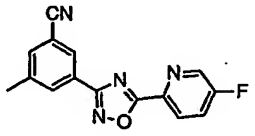
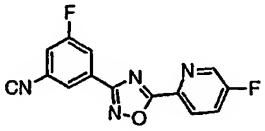
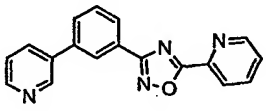
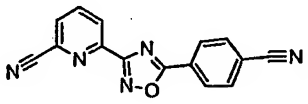
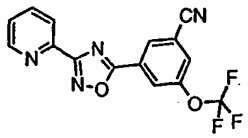
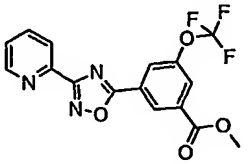
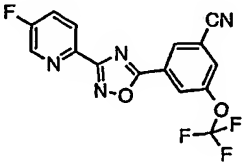
B244	
B167	
B168	
B169	
B170	
B171	
B172	
B173	
B174	

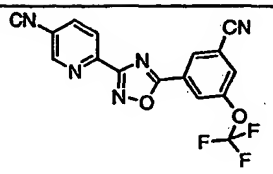
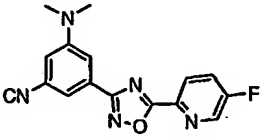
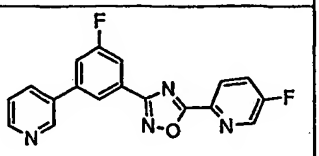
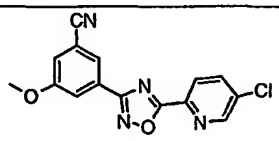
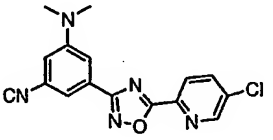
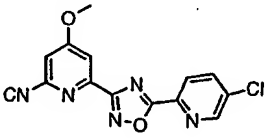
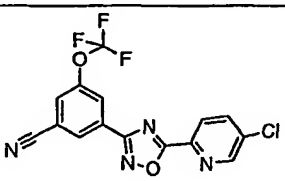
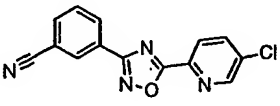
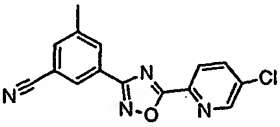
B175	
B245	
B246	
B247	
B260	
B261	
B263	
B262	
B259	

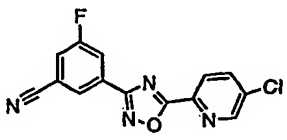
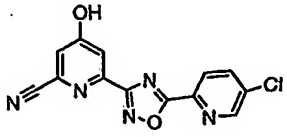
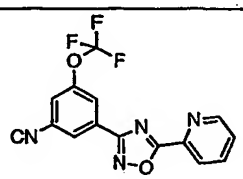
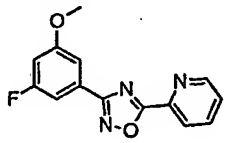
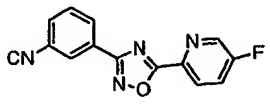
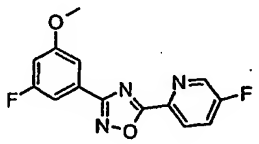
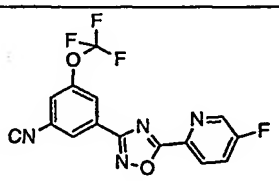
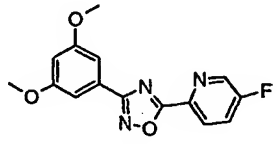
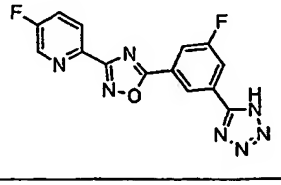
B264	
B274	
B275	
B276	
B277	
B278	
B279	
B280	
B220	

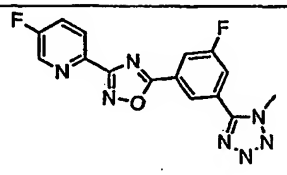
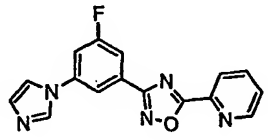
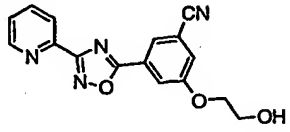
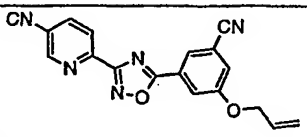
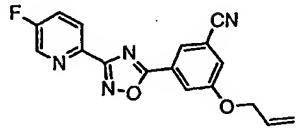
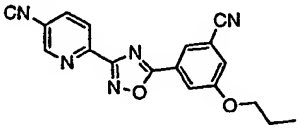
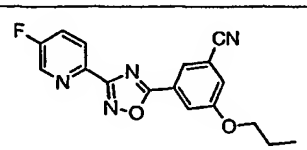
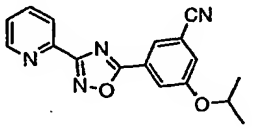
B221	
B265	
B267	
B266	
B268	
B270	
B271	
B222	
B176	

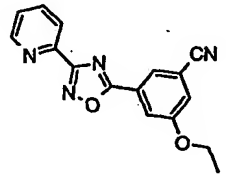
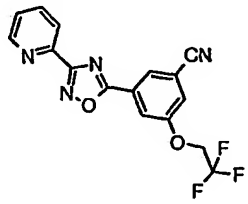
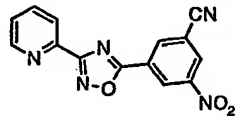
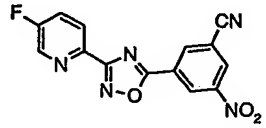
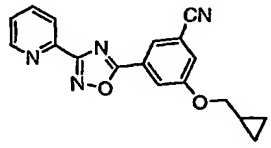
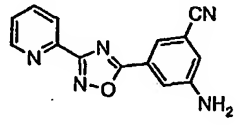
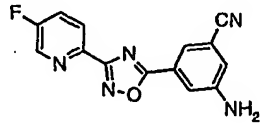
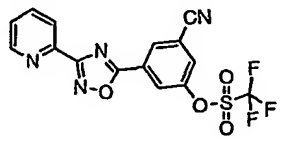
B177	
B225	
B226	
B227	
B181	
B182	
B228	
B183	
B184	

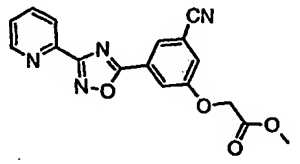
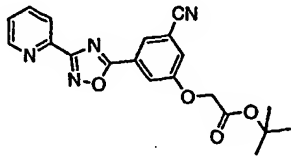
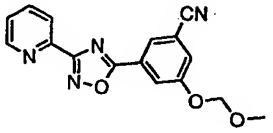
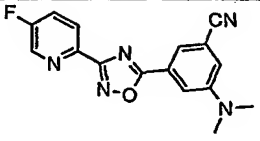
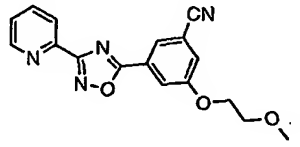
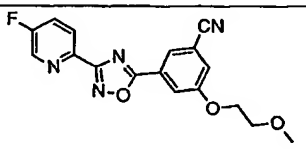
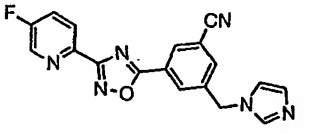
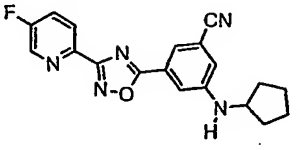
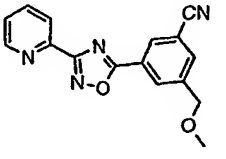
B186	
B187	
B188	
B189	
B229	
B190	
B191	
B192	
B193	

B194	
B195	
B230	
B197	
B196	
B198	
B200	
B201	
B202	

B203	
B199	
B204	
B205	
B206	
B208	
B207	
B209	
B248	

B249	
B210	
B231	
B157	
B158	
B159	
B160	
B232	

B233	
B234	
B161	
B162	
B235	
B236	
B237	
B238	

B239	
B240	
B241	
B163	
B242	
B164	
B165	
B243	
B166	

Preparation of mGluR Group I antagonists

Many starting materials for preparing the compounds of the present invention are available from commercial sources, such as Aldrich Chemical Company (Milwaukee, WI). Moreover, compounds of the invention are readily prepared, from available precursors, using straightforward transformations which are well known in the art. The skilled artisan will recognize that mGluR Group I antagonists, according to the invention, can be prepared via methodology that is well known, using widely recognized techniques of organic chemistry. Suitable reactions are described in standard textbooks of organic chemistry. For example, see March, ADVANCED ORGANIC CHEMISTRY, 2d ed., McGraw Hill (1977).

More specifically, compounds of the invention generally can be prepared by formation of the G moiety between two precursor compounds containing suitable Ar^1 and Ar^2 moieties. When the linker contains a 1,2,4-oxadiazole, the heterocycle may be formed using well known techniques, such as reaction between an amidoxime and an acid chloride, or by the reaction of an amidoxime and an acylimidazole. An illustration of such a transformation is provided in Examples 4 and 5, below.

Amidoximes can be prepared using well known techniques by the reaction of an Ar^1 substituted nitrile with hydroxylamine. An illustration of such a transformation is provided below in Example 1.

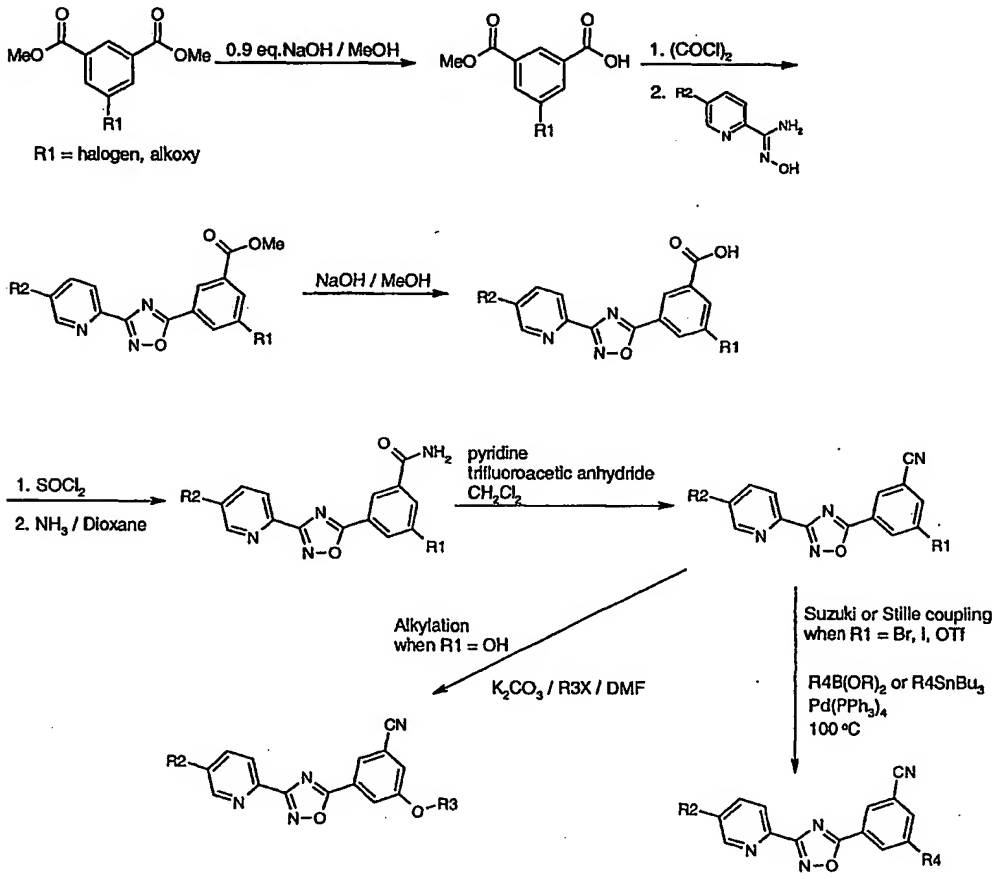
In most cases, the precursor Ar^2 acid chlorides are readily available, or may be prepared using straightforward techniques of organic chemistry. For example, carboxylic acids may be converted into the corresponding acid chlorides by reaction with, for example, thionyl chloride or oxalyl chloride.

In the case where the linker contains a 1,3-oxazole, compounds were prepared using a procedure similar to that given by Kelly et al., J. Org. Chem. 61, 4623-4633 (1996). Thus, 3,5-disubstituted–1,3-oxazoles were prepared by mixing a haloketone with carboxamide in refluxing toluene for 3 days. The resulting

mixture was allowed to cool to room temperature, the solvent was removed and the residue was purified.

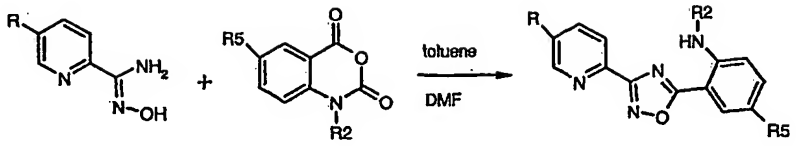
Scheme 1 illustrates a method for synthesizing compounds of the present invention. In particular, the method illustrated by scheme 1 is used for making the following exemplified compounds: B77-B81, B86, B89, B101, B108, B115, B120-B122, B124, B129-B141.

Scheme 1



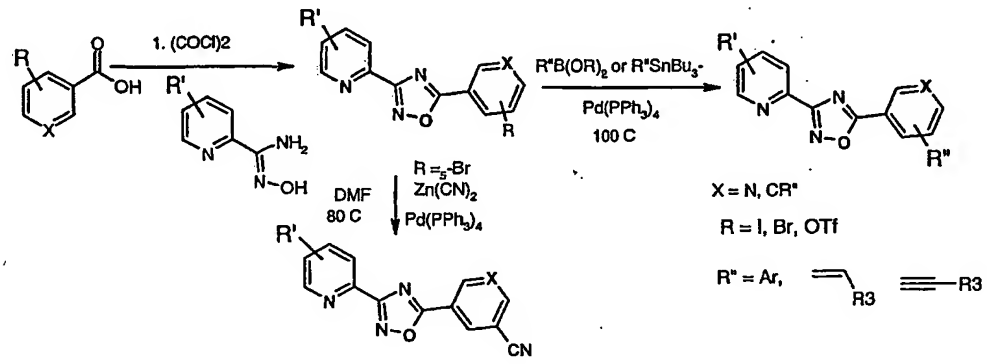
Scheme 2 illustrates another method for synthesizing compounds of the present invention. In particular, the method of scheme 2 is used to make the exemplified compound B144.

Scheme 2



Scheme 3 illustrates a further method for synthesizing compounds of the present invention. In particular, the method of scheme 3 is used to make the following exemplified compounds: B57-B76, B82-B85, B87, B88, B90, B91, B93-B100, B102-B107, B109-B114, B116-B119, B123, B125-B128, B142, B143.

Scheme 3



Other compounds of the present invention may readily be prepared by modifications to the reactions exemplified in the Schemes above, as will be appreciated by the skilled artisan.

EXAMPLES

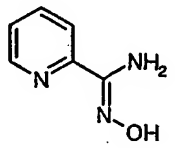
General Experimental Methods

Capillary gas chromatographic and mass spectral data were obtained using a Hewlett-Packard (HP) 5890 Series II Gas Chromatograph coupled to an HP 5971 Series Mass Selective Detector [Ultra-2 Ultra Performance Capillary Column (crosslinked 5% PhMe silicone); column length, 25 m; column i.d., 0.20 mm; helium flow rate, 60 mL/min; injector temp., 250 °C; temperature program, 20 °C/min from 125 to 325 °C for 10 min, then held constant at 325 °C for 6 min]. Thin-layer chromatography was performed using Analtech Uniplate 250-μm silica gel HF TLC plates. UV light sometimes in conjunction with ninhydrin and

Dragendorff's spray reagents (Sigma Chemical Co.) were used for detecting compounds on the TLC plates. Most reagents used in reactions were purchased from the Aldrich Chemical Co. (Milwaukee, WI), Sigma Chemical Co. (Saint Louis, MO), Fluka Chemical Corp. (Milwaukee, WI), Fisher Scientific (Pittsburgh, PA), TCI America (Portland, OR), or Lancaster Synthesis (Windham, NH).

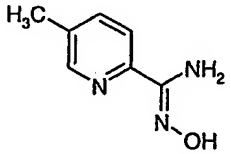
Example 1: Synthesis of Amidoxime Intermediates

Pyrid-2-ylamidoxime



Using the general procedure of Shine et al., *J. Heterocyclic Chem.* (1989) *26*:125-128, hydroxylamine hydrochloride (7.65 g, 110 mmol) in ethanol (100 mL) was treated with a 10N solution of sodium hydroxide (11 mL, 110 mmol). A precipitate quickly formed and the reaction mixture was stirred at room temperature for 30 min. The inorganic precipitate was filtered and rinsed with ethanol (100 mL). The filtrate and ethanol washings were combined and treated with 2-cyanopyridine (10.4 g, 100 mmol). The reaction mixture was then heated at reflux for 20 hours. After cooling, the volatiles were removed *in vacuo*, to afford 13.3 g (97%) of pyrid-2-ylamidoxime.

5-Methyl-pyrid-2-ylamidoxime

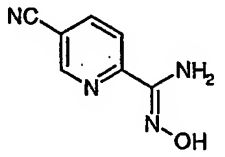


A mixture of 2-bromo-5-methylpyridine (2.001 g, 11.63 mmol), zinc cyanide (830 mg, 7 mmol), zinc (dust, 35 mg, 0.53 mmol), [1,1'-bis(diphenylphosphino)ferrocene] dichloropalladium(II), complex with dichloromethane (1:1) (192.5 mg, 0.24 mmol) in *N,N*-dimethylformamide (10 mL) was heated at reflux for 16 hours. After cooling, the reaction was diluted with ethyl acetate and extracted with water and brine. The organic solution was filtered

through a plug of silica gel, washing dichloromethane. Removal of the solvent *in vacuo*, afforded 770 mg (56%) of 5-methyl-2-cyano-pyridine.

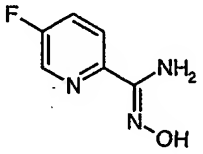
Using the general procedure for the synthesis of amidoximes, 5-methyl-2-cyano-pyridine (770 mg, 6.5 mmol), 5M hydroxylamine hydrochloride (1.5 mL, 7.5 mmol) in ethanol (10 mL), and 10*N* sodium hydroxide (0.75 mL, 7.5 mmol), were heated at reflux for 18 hours. Standard work up afforded 594 mg (60%) of 5-methylpyrid-2-ylamidoxime.

5-Cyanopyrid-2-ylamidoxime



In a similar fashion, a mixture of 2,5-dicyanopyridine (740mg, 5.74 mmol), 5M hydroxyamine hydrochloride (1.15 mL, 5.75 mmol) and 1M sodium hydroxide (5.74 mL, 5.74 mmol) in ethanol (10 mL) was heated at 80 °C for 5 minutes. The precipitate was collected by filtration to afford 555 mg (60%) of 5-cyanopyrid-2-ylamidoxime.

5-Fluoropyrid-2-ylamidoxime

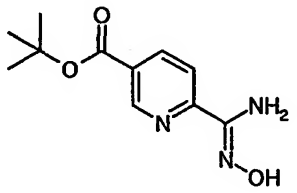


A mixture of 2-cyano-5-chloropyridine (1 g, 7.22 mmol) and potassium fluoride (1.26 g, 21.68 mmol) in 1-methyl-2-pyrrolidinone (25 mL) was heated at reflux for 18 hours. After cooling, the reaction was diluted with ethyl acetate and extracted with water and brine. The organic solvents were then removed *in vacuo*. Silica gel chromatography of the residue afforded 425 mg (48%) of 2-cyano-5-fluoropyridine.

Using the general procedure for the synthesis of amidoximes, 2-cyano-5-fluoropyridine (425 mg, 3.48 mmol), 5M hydroxylamine hydrochloride (0.79 ml, 3.95 mmol) in ethanol (5 mL), and 10*N* sodium hydroxide (0.398 mL, 3.98 mmol)

were heated at reflux for 24 hours. Standard work up afforded 330 mg (61%) of 5-fluoropyrid-2-ylamidoxime.

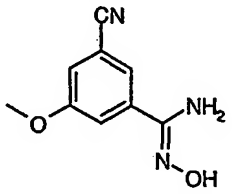
5-Tert-Butoxycarbonyl-pyrid-2-ylamidoxime



A suspension of 6-cyanonicotinic acid (535 mg, 3.6 mmol) in dichloromethane (8 mL) at 0 °C was treated with 2M oxalyl chloride (3.6 mL, 7.2 mmol, dichloromethane) and a catalytic amount of *N,N*-dimethylformamide. The reaction was then stirred at room temperature for 2 hours. The solvent was removed *in vacuo* and the residue dissolved in dichloromethane (10 mL). The resulting solution was treated with pyridine (2 mL) and tert-butanol (0.8 mL) and the reaction mixture stirred overnight at room temperature. The reaction mixture was diluted with dichloromethane (200 mL) and washed sequentially with saturated sodium bicarbonate (50 mL) and brine (50 mL). The organic layer was dried over anhydrous sodium sulfate, filtered and the solvent removed *in vacuo*. Silica gel chromatography, using a gradient of 5% to 10% ethyl acetate in hexane, afforded 623 mg (84%) of 5-tert-butoxycarbonyl-2-cyano-pyridine, as a yellow solid.

Using the general procedure for the synthesis of amidoximes, 5-tert-butoxycarbonyl-2-cyano-pyridine (623 mg, 3.05 mmol) and 5M hydroxylamine hydrochloride (0.69 mL, 3.4 mmol) in ethanol (7 mL) and 10*N* sodium hydroxide (0.34 mL, 3.4 mmol), were heated at reflux for 18 hours. Standard work up afforded 570 mg (79%) of 5-tert-butoxycarbonylpyrid-2-ylamidoxime.

3-Cyano-5-methoxypyrid-2-ylamidoxime



A solution of dimethyl-5-hydroxyisophthalate (6 g, 28.6 mmol) and potassium carbonate (9 g, 65.4 mmol) in acetone (120 mL) was prepared. To this, methyl iodide (4 mL, 63.7 mmol) was added and the reaction was left stirring overnight at ambient temperature. The reaction mixture was filtered and then concentrated. The residue was dissolved in ethyl acetate and washed with water and saturated brine, dried over anhydrous sodium sulfate, filtered, and concentrated. 6.4 g (quantitative) of dimethyl-5-methoxy-isophthalate was isolated as an off-white solid.

A solution of dimethyl-5-methoxy-isophthalate (2.5 g, 11.1 mmol) in tetrahydrofuran/methanol (56 mL/20 mL) was treated with 2.0 N sodium hydroxide (12 mL, 25 mmol). The reaction was left stirring for 15 hours at room temperature. After the solution was concentrated, the solid was dissolved in water and acidified with 2.0 N hydrogen chloride. Ethyl acetate was used to extract the precipitate, which was then washed with brine and dried over anhydrous sodium sulphate. After removal of solvent *in vacuo*, a total of 2.5 g (quantitative) of 5-methoxyisophthalic acid was isolated.

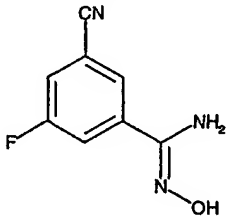
A solution of 5-methoxyisophthalic acid (2.5g, 13.8 mmol) in dichloromethane (20 mL) was treated with 2M oxalyl chloride (38 mL, 76.6mmol) and a few drops of DMF. After stirring for 17 hours, the reaction was concentrated *in vacuo* and then the resulting brown oil was transferred into a cold, stirred solution of ammonium hydroxide in ethyl acetate (70mL/200mL) with a small amount of dichloromethane. The reaction was allowed to proceed for 1 hour, after which a precipitate formed. Water (100 mL) and ethyl acetate (1500 mL) were combined with the reaction in a separatory funnel, and the organic layer was collected, washed with brine and dried over sodium sulphate. The remaining solid in the aqueous layer was isolated by filtration, washed with water, and dried. The

organic layer was filtered and concentrated and then triturated with hexanes. A total of 2.5g (quantitative) of the 5-methoxyisophthalamide was isolated.

A suspension of the 5-methoxyisophthalamide (3.1 g, 16 mmol) in a dichloromethane (27 mL) at 0 °C was treated with pyridine (5.2 mL, 65 mol) and then trifluoroacetic anhydride drop-wise (5.4 mL, 39 mmol). The reaction was stirred at 0 °C for 20 minutes and then stirred overnight at ambient temperature. The reaction mixture was washed with water and saturated brine, dried over anhydrous sodium sulfate, filtered and concentrated. Silica gel chromatography using hexanes:ethyl acetate:dichloromethane afforded 940 mg (46%) of the 5-methoxyisophthalonitrile as a white solid.

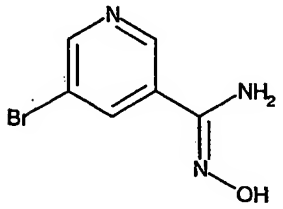
Using the general procedure for the synthesis of amidoximes, 5-methoxyisophthalonitrile (600 mg, 3.8 mmol), 5M hydroxylamine hydrochloride (0.76 ml, 3.8 mmol) in ethanol (6 mL), and 1*N* sodium hydroxide (3.8 mL, 3.8 mmol) were heated at reflux for 3 hours. Standard work up and column chromatography using 30-40 % ethyl acetate/hexanes afforded 329 mg (45%) of 3-cyano-5-methoxyphenyl-amidoxime.

3-Cyano-5-fluorophenylamidoxime



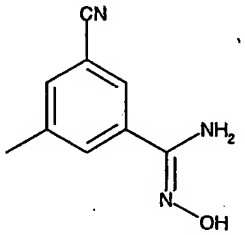
5-Fluoro-isophthalonitrile (730 mg, 5 mmol) and 5M hydroxylamine hydrochloride (1 mL, 5 mmol) in ethanol (10 mL) and 1 *N* sodium hydroxide (5 mL, 5 mmol), were heated at reflux for 30 minutes. Standard work up followed by column chromatography afforded 473 mg (52.8%) of 3-cyano-5-fluorophenylamidoxime

5-Bromopyrid-3-yl-amidoxime



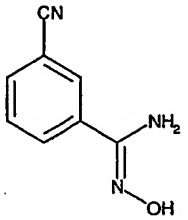
5-Bromonicotinonitrile (982 mg, 5.4 mmol) and 5M hydroxylamine hydrochloride (1.098 mL, 5.4 mmol) in ethanol (5 mL) and 1 *N* sodium hydroxide (5.4 mL, 5.4 mmol), were heated at reflux for 5 minutes. Standard work up afforded 925 mg (79.3%) of 5-bromopyrid-3-yl-amidoxime.

3-Cyano-5-methylphenylamidoxime



3,5-Dicyanotoluene (1000 mg, 7.04 mmol) and 5M hydroxylamine hydrochloride (1.4 mL, 7.04 mmol) in ethanol (5 mL) and 1 *N* sodium hydroxide (7.04 mL, 7.04 mmol), were heated at reflux for 12 minutes. Standard work up followed by column chromatography afforded 215 mg (17.4%) of 3-cyano-5-methylphenylamidoxime.

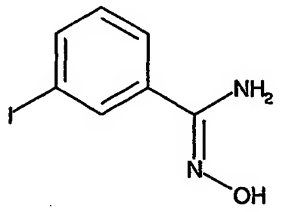
3-Cyanophenylamidoxime



Isophthalonitrile (640 mg, 5 mmol) and 5M hydroxylamine hydrochloride (1 mL, 5 mmol) in ethanol (5 mL) and 1 *N* sodium hydroxide (5 mL, 5 mmol), were

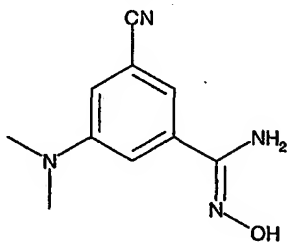
heated at reflux for 2.5 hours. Standard work up followed by column chromatography afforded 650 mg (80.7%) of 3-cyanophenylamidoxime.

3-Iodophenylamidoxime



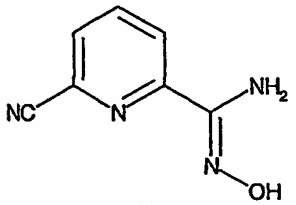
3-Iodobenzonitrile (1145 mg, 5 mmol) and 5M hydroxylamine hydrochloride (1 mL, 5 mmol) in ethanol (5 mL) and 1 *N* sodium hydroxide (5 mL, 5 mmol), were heated at reflux for 2.5 hours. Standard work up followed by column chromatography afforded 920 mg (70.2%) of 3-iodophenylamidoxime.

3-Cyano-5-dimethylaminophenylamidoxime



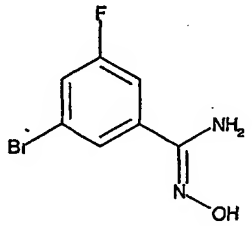
5-Dimethylaminoisophthalonitrile (856 mg, 5 mmol) and 5M hydroxylamine hydrochloride (1 mL, 5 mmol) in ethanol (10 mL) and 1 *N* sodium hydroxide (5 mL, 5 mmol), were heated at reflux for 30 minutes. Standard work up followed by column chromatography afforded 280 mg (27.4%) of 3-cyano-5-dimethylaminophenylamidoxime.

6-Cyano-pyrid-2-yl-amidoxime



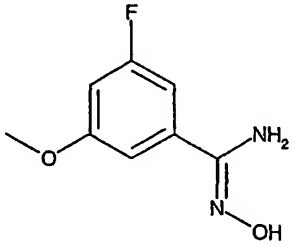
2,6-Dictanopyridine (3.87 g, 30 mmol) and 5M hydroxylamine hydrochloride (6 mL, 30 mmol) in ethanol (50 mL) and 1 *N* sodium hydroxide (30 mL, 30 mmol), were heated at reflux for 10 minutes. Standard work up followed by column chromatography afforded 2.87 g (59%) of 6-cyano-pyrid-2-yl-amidoxime.

3-Bromo-5-fluorophenylamidoxime



3-Bromo-5-fluorobenzonitrile (1.9 g, 9.5 mmol) and 5M hydroxylamine hydrochloride (4 mL, 20 mmol) in ethanol (20 mL) and 1 *N* sodium hydroxide (20 mL, 20 mmol), were heated at reflux for 1 hour. Standard work up followed by column chromatography afforded 721 mg (32.6%) of 3-bromo-5-fluorophenylamidoxime.

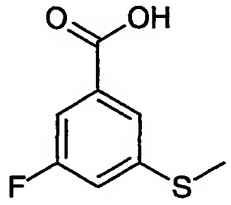
3-Fluoro-5-methoxyphenylamidoxime



3-Fluoro-5-methoxybenzonitrile (379 mg, 2.5 mmol) and 5M hydroxylamine hydrochloride (0.5 mL, 2.5 mmol) in ethanol (2.5 mL) and 1 *N* sodium hydroxide

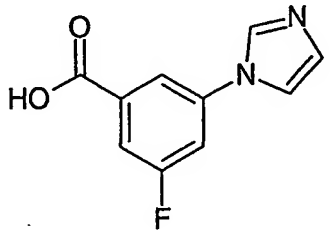
(2.5 mL, 2.5 mmol), were heated at reflux for 1 hour. Standard work up afforded 431 mg (93.4%) of 3-fluoro-5-methoxyphenylamidoxime.

5-fluoro-3-(thiomethyl)benzoic acid



1-Bromo-3,5-difluorobenzene (1.00 g, 5.18 mmol) was dissolved in anhydrous DMF (10 mL). The solution was chilled in an ice bath, and NaSMe (0.36 g, 5.18 mmol) was added. After 30 minutes the reaction mixture was poured into water (100 mL) and extracted with hexanes. The organic phase was washed with water and brine, dried ($MgSO_4$), filtered, and concentrated to provide the title compound as a colourless oil. The crude product was used directly in the next step. Using the standard cyanation procedure, 5-cyano-3-fluoro-1-(thiomethyl)benzene was prepared as a yellow oil. The crude product was used directly in the next step. Using the standard saponification procedure, the title compound was prepared in 0.60 g yield (63% over 3 steps) as a colourless solid.

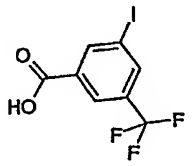
3-Fluoro-5-(1*H*-imidazol-1-yl)benzoic acid



1-Bromo-3,5-difluorobenzene (1.00 g, 5.18 mmol) was dissolved in anhydrous DMF (10 mL). The solution was chilled in an ice bath. Imidazole (0.36 g, 5.18 mmol) and K_2CO_3 (0.72 g, 5.18 mmol) were added. The reaction mixture was stirred at room temperature for 16 hours, and at 80 °C for 24 hours. The reaction mixture was poured into water (100 mL) and extracted with EtOAc. The

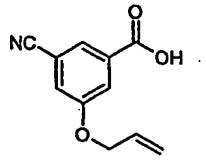
organic phase was washed with brine, dried ($MgSO_4$), filtered, and concentrated. The intermediate 3-Fluoro-5-Bromo-(1H-imidazol-1-yl)-benzene was used directly in the next step. Using the standard cyanation procedure, 3-Fluoro-5-cyano-(1H-imidazol-1-yl)-benzene was prepared as a colourless solid. The crude product was used directly in the next step. Using the standard saponification procedure, the title compound was prepared as a colourless solid. The crude product was used directly in the next step.

3-Iodo-5-Trifluoromethylbenzoic acid



The title product was prepared according to the literature procedure (Fujiki, Kanji; Kashiwagi, Mitsuyoshi; Miyamoto, Hideyuki; Sonoda, Akinari; Ichikawa, Junji; et al *J.Fluorine Chem.* **1992**, *57*, 307-321) from 3,5-bis(trifluoromethyl)benzene (7.3 mL, 47 mmol) and iodine (11.95 g, 47 mmol) in 30% oleum (30 mL) at 55 degrees for 15h. Quenching with ice was followed by extraction of the crude product into ether, sequential washing of the aqueous layer with sodium sulfite (1M) and water. Sodium hydroxide (!N, ~150 mL) was added to the crude ether solution until pH basic, the layers were separated and the aqueous layer was then acidified using HCl (12N, ~10 mL, pH acidic). Extraction into ether followed by drying over magnesium sulfate yielded the crude acid (4.3 g, 29%). The material was insufficiently pure for use, so the product was esterified using acetyl chloride in methanol, purified using flash chromatography (silica gel, 20% dichloromethane in hexane) and hydrolyzed with sodium hydroxide in methanol yielding 2.95 g (69%) of pure 3-iodo-5-Trifluoromethylbenzoic acid.

3-Allyloxy-5-cyanobenzoic acid

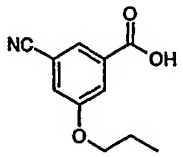


A suspension of 3-allyloxy-5-(methoxycarbonyl)benzoic acid (5.5 mg, 23 mmol) in thionyl chloride (30 mL) was heated at reflux for 2 hours. The excess thionyl chloride was then removed *in vacuo* and the intermediate acid chloride dissolved in dichloromethane (25 mL). After cooling to 0 °C the solution was treated with 0.5 M ammonia in 1,4-dioxane (100 mL) and then allowed to warm to room temperature. After 2 hours of stirring the solvent was removed *in vacuo* and the residue was titurated with water. The precipitate was collected, washed with water, and dried *in vacuo* to afford the 5.0 g (92 %) of methyl 3-(allyloxy)-(5-aminocarbonyl)benzoate as a white solid.

A suspension of methyl 3-(allyloxy)-(5-aminocarbonyl)benzoate (5.0 g, 21 mmol) in a dichloromethane (70 mL) at 0 °C was treated with pyridine (3.5 mL, 43 mmol) and then trifluoroacetic anhydride drop-wise (3.6 mL, 25 mmol). The reaction was stirred at 0 °C for 20 minutes and then stirred overnight at ambient temperature. The reaction mixture was washed with water and saturated brine, dried over anhydrous sodium sulfate, filtered and concentrated. Silica gel chromatography using a 10 % ethyl acetate/hexanes afforded 3.8 g (81%) of methyl 3-(allyloxy)-5-cyanobenzoate as a white solid.

A solution of methyl 3-(allyloxy)-5-cyanobenzoate (1.5 g, 6.9 mmol) in methanol-tetrahydrofuran (1:2, 30 mL) was treated with 0.5 N lithium hydroxide (17 mL, 8.3 mmol). The reaction was stirred at 70°C for 30 minutes and then the solvent was removed *in vacuo*. The residue was dissolved in a small amount of water and then acidified (pH ~ 4) by the addition of 2N hydrogen chloride. The precipitate was collected and dried to afford 1.0 g (74%) of 3-allyloxy-5-cyanobenzoic acid as a white solid.

3-Cyano-5-propoxybenzoic acid



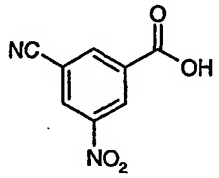
A suspension of 3-allyloxy-5-(methoxycarbonyl)benzoic acid (5.5 mg, 23 mmol) in thionyl chloride (30 mL) was heated at reflux for 2 hours. The excess thionyl chloride was then removed in vacuo and the intermediate acid chloride dissolved in dichloromethane (25 mL). After cooling to 0 °C the solution was treated with 0.5 M ammonia in 1,4-dioxane (100 mL) and then allowed to warm to room temperature. After 2 hours of stirring the solvent was removed in vacuo and the residue was titurated with water. The precipitate was collected, washed with water, and dried *in vacuo* to afford the 5.0 g (92 %) of methyl 3-(allyloxy)-(5-aminocarbonyl)benzoate as a white solid.

Methanol (20 mL) and dichloromethane (20 mL) were added to round bottom flask that contained methyl 3-(allyloxy)-(5-aminocarbonyl)benzoate (2.0 g, 8.5 mmol) and palladium(10 wt.% on activated carbon, 200 mg) under argon. The flask was evacuated using a water aspirator and then filled with hydrogen from a balloon. The balloon filled was hydrogen was attached to the flask as the reaction stirred for 2 hours. The palladium on carbon was remove by filtration through celite. The solvent was removed using a roto-evaporator and then the sample was dried under vacuum to afford 2.0 (97%) of methyl 3-(aminocarbonyl)-5-propoxybenzoate as a white solid.

A suspension of methyl 3-(aminocarbonyl)-5-propoxybenzoate (2.0 g, 8.2 mmol) in a dichloromethane (25 mL) at 0 °C was treated with pyridine (1.3 mL, 17 mmol) and then trifluoroacetic anhydride dropwise (1.4 mL, 9.9 mmol). The reaction was stirred at 0 °C for 20 minutes and then stirred overnight at ambient temperature. The reaction mixture was washed with water and saturated brine, dried over anhydrous sodium sulfate, filtered and concentrated. Silica gel chromatography using a 40 % dichloromethane/hexanes afforded 1.5 g (84%) of methyl 3-cyano-5-propoxybenzoate as a white solid.

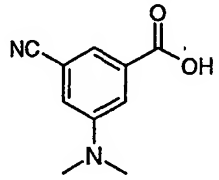
A solution of methyl 3-cyano-5-propoxybenzoate (1.5 g, 6.8 mmol) in methanol-tetrahydrofuran (1:2, 30 mL) was treated with 0.5 M lithium hydroxide (16 mL, 8.2 mmol). The reaction was stirred at 70°C for 30 minutes and then the solvent was removed *in vacuo*. The residue was dissolved in a small amount of water and then acidified (pH ~ 4) by the addition of 2*N* hydrogen chloride. The precipitate was collected and dried to afford 1.2 g (86%) of 3-cyano-5-propoxybenzoic acid.

3-Cyano-5-nitrobenzoic acid



Using the same procedure as for 3-allyloxy-5-cyanobenzoic acid, 3-cyano-5-nitrobenzoic acid (2.0 g, 10.7 mmol) was prepared from mono-methyl 5-nitroisophthalate (5.0 g, 22 mmol).

3-Cyano-5-dimethylaminobenzoic acid



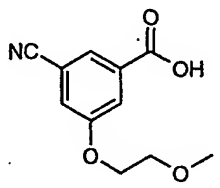
Methyl 3-cyano-2-nitrobenzoate (6.0g, 29 mmol) and tin(II) chloride dihydrate (26 g, 12 mmol) in methanol (100 mL) were heated at reflux for 3 hours. The reaction mixture was transferred into a 1L Erlenmeyer flask equipped with a stirring bar and containing ice. While stirring the reaction mixture, 1N sodium hydroxide was added until pH ~ 4-5. At this point solid sodium bicarbonate was added until pH ~ 8. The mixture was transferred to a separatory funnel and extracted with ethyl acetate. The organic layer was washed with water and saturated brine, dried over anhydrous sodium sulfate, filtered and concentrated.

Silica gel chromatography using 30 % ethyl acetate/hexanes afforded 2.4 g (47%) of methyl 3-amino-5-cyanobenzoate as a light brown solid.

Formaldehyde, 37 wt. % solution in water, (4.3 mL, 57 mmol), solid sodium cyanoborohydride (752 mg, 11 mmol), and then acetic acid (909 µL, 16 mmol) were added to methyl 3-amino-5-cyanobenzoate (500 mg, 2.8 mmol) in acetonitrile (10 mL). After stirring at ambient temperature for 5 hours, the reaction mixture was transferred to a separatory funnel and then ethyl acetate was added. The organic layer was washed with water and saturated brine, dried over anhydrous sodium sulfate, filtered, and concentrated. Silica gel chromatography using 15% ethyl acetate/hexanes afforded 390 mg (55%) methyl-3-cyano-5-dimethylaminobenzoate.

A solution of methyl-3-cyano-5-dimethylaminobenzoate (318 mg, 1.6 mmol) in tetrahydrofuran (5 mL) was treated with 0.5 N lithium hydroxide (3.7 mL, 1.9 mmol). The reaction was stirred at 70°C for 30 minutes and then the solvent was removed *in vacuo*. The residue was dissolved in a small amount of water and then acidified by the dropwise addition of 2 *N* hydrogen chloride until a white precipitate no longer formed. Following extraction of the aqueous layer with diethyl ether, the organic layer was then washed with water and saturated brine, dried over anhydrous sodium sulfate, filtered, and concentrated to afford 308 mg (quantitative) of 3-cyano-5-dimethylaminobenzoic acid.

3-cyano-5-(2-methoxyethoxy)benzoic acid



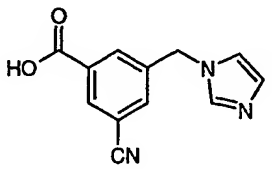
A mixture of methyl 3-allyloxy-5-cyanobenzoate (1.5 g, 6.9 mmol) and tetrabutylammonium iodide (2.8 g, 7.6 mmol) in dichloromethane (38 mL) at –78 °C, under argon, was treated with a solution of 1M boron trichloride in dichloromethane (24 mL, 24 mmol). After 5 minutes at –78 °C, the reaction mixture was stirred at ambient temperature for 1 hour. The reaction was then

quenched with ice water and stirred for an additional 30 minutes. The organic layer was washed with saturated sodium bicarbonate, dried over anhydrous sodium sulfate, filtered and concentrated. Silica gel chromatography using a gradient of 20-30% ethyl acetate/hexanes afforded 811 mg (67%) of methyl 3-cyano-5-hydroxybenzoate as a light yellow solid.

A mixture of methyl 3-cyano-5-hydroxybenzoate (302 mg, 1.7 mmol), potassium carbonate (471 mg, 3.4 mmol) and 2-chloroethyl methyl ether (309 µL mg, 3.4 mmol) in *N,N*-dimethylformamide (4 mL) was heated in a sealed vial at 140 °C for 15 minutes. The reaction was cooled, diluted with ethyl acetate, washed with water and saturated brine, filtered and concentrated. Filtration through silica gel using dichloromethane afforded 375 mg (93%) of methyl 3-cyano-5-(2-methoxyethoxy)benzoate.

A solution of methyl 3-cyano-5-(2-methoxyethoxy)benzoate (375 mg, 1.6 mmol) in tetrahydrofuran (4 mL) was treated with 0.5 N lithium hydroxide (3.8 mL, 1.9 mmol). The reaction was stirred at 70°C for 30 minutes and then the solvent was removed *in vacuo*. The residue was dissolved in a small amount of water and then acidified with 2 *N* hydrogen chloride until pH ~ 2. Following extraction of the aqueous layer with ethyl acetate, the organic layer washed with water and saturated brine, dried over anhydrous sodium sulfate, filtered, and concentrated to afford 343 mg (97%) of 3-cyano-5-(2-methoxyethoxy)benzoic acid.

3-cyano-5-(1H-imidazol-1-yl-methyl)benzoic acid



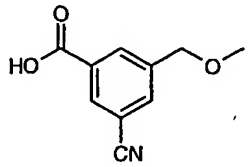
A mixture of methyl 3-(bromomethyl)-5-iodobenzoate (500 mg, 1.4 mmol), potassium carbonate (388 mg, 2.8 mmol), and imidazole (96 mg, 1.4 mmol) in *N,N*-dimethylformamide (4 mL) was heated at 70 °C for 3 hours. After cooling, the reaction mixture was diluted with water and then extracted with dichloromethane. The organic layer was washed with water and saturated brine, dried over

anhydrous sodium sulfate, filtered, and concentrated. Silica gel chromatography using 100% ethyl acetate afforded 242 mg (51%) of methyl 3-(imidazol-1-ylmethyl)-5-iodobenzoate as a white solid.

After bubbling argon into a solution of methyl 3-(imidazol-1-ylmethyl)-5-iodobenzoate (242 mg, 0.70 mmol) in N,N-dimethylformamide (2 mL) for 5 minutes, zinc cyanide (90 mg, 0.77 mmol) and tetrakis(triphenylphosphine)palladium(0) (80 mg, 0.070 mmol) were added. The reaction mixture was heated at 80°C for 30 minutes under argon. Following cooling, the reaction mixture was diluted with ethyl acetate and then the precipitate that formed was removed by filtration. The filtrate was washed with water and saturated brine, dried over anhydrous sodium sulfate, filtered, and concentrated. The residue was triturated with 20 % diethyl ether/hexanes, filtered, and dried in vacuo to afford 150 mg (89%) of 3-cyano-5-(1H-imidazol-1-yl-methyl)benzoate as a white solid.

A solution of 3-cyano-5-(1H-imidazol-1-yl-methyl)benzoate (150 mg, 0.62 mmol) in tetrahydrofuran (2 mL) was treated with 0.5 N lithium hydroxide (1.5 mL, 0.75 mmol). The reaction was stirred at 70°C for 10 minutes and then the solvent was removed *in vacuo*. The residue was dissolved in a small amount of water and then acidified (pH ~ 4) by the addition of 2*N* hydrogen chloride. The precipitate was collected and dried to afford 140 mg (quantitative) of 3-cyano-5-(1H-imidazol-1-yl-methyl)benzoic acid.

3-cyano-5-(methoxymethyl)benzoic acid



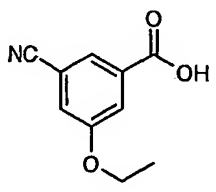
A mixture of methyl 3-(bromomethyl)-5-iodobenzoate (400 mg, 1.1 mmol) and potassium carbonate (311 mg, 2.3 mmol) in methanol/tetrathydrofuran (5 mL/5 mL) was heated at 55 °C for 1 hour. After cooling, the reaction mixture was diluted with water and then extracted with ethyl acetate. The organic layer was

washed with water and saturated brine, dried over anhydrous sodium sulfate, filtered, and concentrated. After drying in vacuo, 325 mg (94%) of methyl 3-(methoxymethyl)-5-iodobenzoate was isolated as a white solid.

After bubbling argon into a solution of methyl 3-(methoxymethyl)-5-iodobenzoate (316 mg, 1.03 mmol) in N,N-dimethylformamide (3 mL) for 5 minutes, zinc cyanide (133 mg, 1.13 mmol) and tetrakis(triphenylphosphine)palladium(0) (119 mg, 0.010 mmol) were added. The reaction mixture was heated at 80°C for 15 minutes under argon. Following cooling, the reaction mixture was diluted with ethyl acetate and then the precipitate that formed was removed by filtration. The filtrate was washed with water and saturated brine, dried over anhydrous sodium sulfate, filtered, and concentrated. Silica gel chromatography using 10-30% ethyl acetate/hexanes afforded 184 mg (86%) of methyl 3-cyano-5-(methoxymethyl)benzoate as a colorless oil.

A solution of methyl 3-cyano-5-(methoxymethyl)benzoate (184 mg, 0.75 mmol) in tetrahydrofuran (2.1 mL) was treated with 0.5 N lithium hydroxide (1.8 mL, 0.90 mmol). The reaction was stirred at 70°C for 30 minutes and then after cooling the solvent was removed *in vacuo*. The residue was dissolved in a small amount of water and then acidified with 2 *N* hydrogen chloride until pH ~ 2-3. Following extraction of the aqueous layer with ethyl acetate, the organic layer washed with water and saturated brine, dried over anhydrous sodium sulfate, filtered, and concentrated to afford 145 mg (quantitative) of 3-cyano-5-(methoxymethyl)benzoic acid.

3-cyano-5-ethoxybenzoic acid

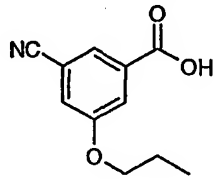


A solution of methyl 3-cyano-5-hydroxybenzoate (270 mg, 1.5 mmol) and potassium carbonate (482 mg, 3.4 mmol) in acetone (5.5 mL) was prepared. To

this, ethyl iodide (272 µL, 3.4 mmol) was added and the reaction was heated at 52°C for 2.5 hours. The reaction mixture was concentrated, re-dissolved in ethyl acetate and washed with water and saturated brine. The organic solvent layer was collected, dried over anhydrous sodium sulphate, filtered, and concentrated. 321 mg (99%) of methyl 3-cyano-5-ethoxybenzoate was isolated as a light brown solid.

Methyl 3-cyano-5-ethoxybenzoate (312 mg, 1.5 mmol) was hydrolyzed as previously described to afford 290 mg (quantitative) of 3-cyano-5-ethoxybenzoic acid as an off-white solid.

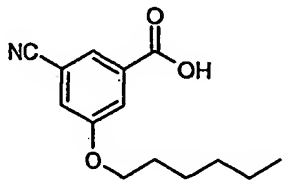
3-cyano-5-propoxybenzoic acid



A solution of methyl 3-cyano-5-hydroxybenzoate (200 mg, 1.3 mmol) and potassium carbonate (357 mg, 2.6 mmol) in acetone (4.0 mL) was prepared. To this, propyl iodide (245 µL, 2.5 mmol) was added and the reaction was heated at 50°C for 5 hours. The reaction mixture was concentrated, re-dissolved in ethyl acetate and washed with water and saturated brine. The organic solvent layer was collected, dried over anhydrous sodium sulphate, filtered, and concentrated. 222 mg (90%) of methyl 3-cyano-5-propoxybenzoate was isolated as a light brown solid.

Methyl 3-cyano-5-propoxybenzoate (222 mg, 1.0 mmol) was hydrolyzed as previously described to afford 169 mg (80%) of 3-cyano-5-propoxybenzoic acid as an off-white solid.

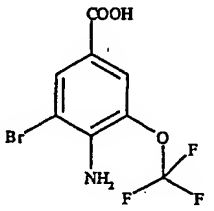
3-cyano-5-hexyloxybenzoic acid



A solution of methyl 3-cyano-5-hydroxybenzoate (170 mg, 0.95 mmol) and potassium carbonate (304 mg, 2.2 mmol) in acetone (4.0 mL) was prepared. To this, 1-bromohexane (300 µL, 2.1 mmol) was added and the reaction was heated at 50°C overnight. The reaction mixture was concentrated, re-dissolved in ethyl acetate and washed with water and saturated brine. The organic solvent layer was collected, dried over anhydrous sodium sulphate, filtered, and concentrated. Trituration with hexanes afforded 250 mg (quantitative) of methyl 3-cyano-5-hexyloxybenzoate as a light brown solid.

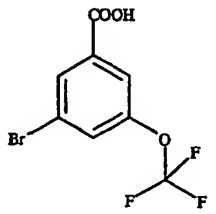
Methyl 3-cyano-5-ethoxybenzoate (250 mg, 0.95 mmol) was hydrolyzed as previously described to afford 247 mg (quantitative) of 3-cyano-5-hexyloxybenzoic acid as an off-white solid.

4-Amino-3-bromo-5-trifluoromethoxybenzoic acid



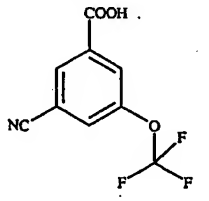
To a solution of 4-amino-3-trifluoromethoxybenzoic acid (5 g, 22.6 mmoles) in acetic acid (50 mL), bromine(3.98 g, 24.9 mmoles) in acetic acid(10 mL) was added dropwise at room temperature. After the reaction mixture was kept stirring for one hour, water was added into the mixture. The solid was filtered and washed with water to give 4-amino-3-bromo-5-trifluoromethoxybenzoic acid (3.9 g, 54.9%).

3-Bromo-5-trifluoromethoxybenzoic acid



4-Amino-3-bromo-5-trifluoromethoxybenzoic acid (1.5 g, 5 mmoles) was mixed with ethanol (15 mL) at 0 °C and then concentrated sulfuric acid (2.26 g, 10.2 mmoles) wad added. The sodium nitrite (0.38 g, 5.5 mmoles) water solution (1.2 mL) was added dropwise at 0 °C for 1 hour. After the reaction mixture was warmed to room temperature and then heated to reflux for 45 minutes, water was added. The mixture was extracted with dichloromethane. The dichloromethane layer was dried and concentrated. The residue was dissolved in 1M sodium hydroxide and extracted with ether. The aqueous solution was acidified with 2M HCl to pH = 2 to give 3-bromo-5-trifluoromethoxybenzoic acid (1.08 g, 75.5%).

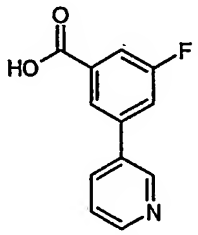
3-Cyano-5-trifluoromethoxybenzoic acid



To an ether solution of 3-bromo-5-trifluoromethoxybenzoic acid (1.08 g, 3.79 mmloes), tirmethylsilylmethyl azide was added in and stirred at room temperature for 10 minutes. The reaction was quenched with methanol and passed column with 2% ethyl acetate in hexanes to give colorless oil (0.84 g). This colorless oil was mixed with zinc cyanide (0.33 g, 2.8 mmoles) and tetrakis(triphenylphosphine)palladium(0) ($Pd(PPh_3)_4$, 467 mg, 0.404 mmol) in N,N-dimethylformamide(10 mL) under argon at 85 °C overnight. The reaction mixture was diluted with dichloromethane and washed with water twice. The dichloromethane layer was dried and concentrated. The residue was mixed with1M sodium hydroxide (8 mL) and methanol (4 mL) and stirred at room temperature for

2 hours. The mixture was acidified with 1M HCl to pH = 1 ~ 2 and extracted with ethyl acetate. The ethyl acetate layer was washed with Brine and concentrated. The residue was passed column with 2% ethyl acetate in hexanes to give 3-cyano-5-trifluoromethoxybenzoic acid, which contained 3-[imino(methoxy)methyl]-5-trifluoromethoxybenzoic acid (3:1, 145 mg, 16.6%)

3-Fluoro-5-(3-pyridyl)benzoic acid

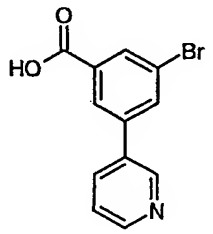


A solution of 3-Bromo-5-fluorobenzoic acid (2.00 g, 9.13 mmol) in thionyl chloride (16 ml) and dimethylformamide (0.4 ml) was stirred at 80°C for 1h. The reaction mixture was concentrated *in-vacuo* and the residue was dissolved in methanol (15 ml) and left stirring at room temperature overnight. The reaction mixture was concentrated *in-vacuo*, and the residue was dissolved in ethyl acetate (50 ml). Organic phase was sequentially washed with water (50 ml), saturated sodium bicarbonate (50 ml, aqueous), water (50 ml) and brine (50 ml), dried (sodium sulfate), filtered and concentrated *in-vacuo* to provide the title compound (1.97 g, 92%) as yellow oil.

To the solution of Methyl-3-bromo-5-fluorobenzoate (1.97 g, 8.44 mmol) in toluene (40 ml) added Pyridine-3-boronic acid-1,3-propanediol ester (1.79 g, 7.63 mmol), potassium carbonate (11.66 g, 84.4 mmol) and tetrakis(triphenylphoshine)palladium (0) (0.49, 0.42 mmol), sequentially. The resulting brownish yellow reaction mixture was heated at 120°C under argon overnight. The reaction mixture was cooled to room temperature, filtered through a pad of celite and concentrated *in-vacuo*. The residue was purified on silica gel using 1% methanol in dichloromethane to isolate the title compound (0.92 g, 47%) as a yellow solid.

In a 100 ml round bottom flask equipped with stir bar added Methyl-3-fluoro-5-(3-pyridyl)benzoate (0.92 g, 3.93 mmol), methanol (10 ml) and sodium hydroxide (5.89 ml, 5.89 mmol, 1N aqueous). Stirred the resulting mixture at 50°C for 2 h. The reaction mixture was cooled to room temperature, concentrated *in-vacuo* and the residue was dissolved in methanol (20 ml). To this mixture added hydrochloric acid (1N diethyl ether) dropwise and stirred at room temperature for 10 min. The reaction mixture was concentrated *in-vacuo* and the residue was triturated with diethyl ether to provide the crude hydrochloride salt of title compound (1.00 g) as an off white solid.

3-Bromo-5-(3-pyridyl)benzoic acid



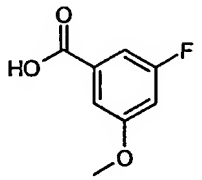
A solution of 3-Bromo-5-iodobenzoic acid (5.00 g, 15.3 mmol) in methanol (30 ml) and hydrochloric acid (15.3 ml, 15.3 mmol, 1N diethyl ether) was stirred at room temperature for 48h. The reaction mixture was concentrated *in-vacuo* and the residue was diluted with dichloromethane (100 ml). The organic phase was sequentially washed with sodium hydroxide (100 ml, 1N aqueous), water (100 ml) and brine (100 ml), dried (sodium sulfate), filtered and concentrated *in-vacuo*. The crude residue was dissolved in 10% ethyl acetate in hexanes (100 ml) and filtered through a pad of silica gel. Upon concentrating *in-vacuo*, isolated the methyl ester (4.98 g, 95%) as yellowish white solid.

To the solution of Methyl-3-bromo-5-iodobenzoate (2.00 g, 5.87 mmol) in toluene (50 ml) added Pyridine-3-boronic acid-1,3-propanediol ester (1.24 g, 7.63 mmol), potassium carbonate (8.11 g, 58.7 mmol) and tetrakis(triphenylphoshine)palladium (0) (0.34, 0.29 mmol), sequentially. The resulting brownish yellow reaction mixture was heated at 80°C under argon for 10 h. The reaction mixture was cooled to room temperature, filtered through a pad of

celite and concentrated *in-vacuo*. The residue was purified on silica gel using 3% methanol in dichloromethane to isolate Methyl-3-bromo-5-(3-pyridyl)benzoate (1.16 g, 67%) as a white solid.

In a 100 ml round bottom flask equipped with stir bar added Methyl-3-bromo-5-(3-pyridyl)benzoate (1.16 g, 3.96 mmol), methanol (15 ml) and sodium hydroxide (5.94 ml, 5.94 mmol, 1N aqueous). Stirred the resulting mixture at 50°C for 2 h. The reaction mixture was cooled to room temperature, concentrated *in-vacuo* and the residue was dissolved in methanol (20 ml). To this mixture added hydrochloric acid (1N diethyl ether) dropwise and stirred at room temperature for 10 min. The reaction mixture was concentrated *in-vacuo* and the residue was triturated with diethyl ether to provide the crude hydrochloride salt of title compound (1.50 g) as a white solid.

3-Fluoro-5-methoxybenzoic acid

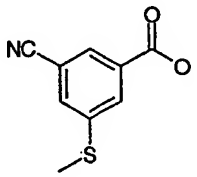


In a 250 ml round bottom flask equipped with stir bar added 3,5-Difluorobenzonitrile (4.2 g, 30.4 mmol), sodium methoxide (10.4 ml, 45.6 mmol, 25% methanol) and dimethylformamide (40 ml). Stirred the resulting reaction mixture at room temperature, overnight. The reaction mixture was concentrated *in-vacuo* and residue was dissolved in dichloromethane (200 ml). The organic phase was washed sequentially with water (150 ml) and brine (150 ml), dried (sodium sulfate) and concentrated *in-vacuo*. The crude residue was purified on silica gel using 10% diethyl ether in hexanes to isolate 3-Fluoro-5-methoxybenzonitrile (1.63 g) as a white solid.

In a 50 ml round bottom flask equipped with stir bar and reflux condensor added 3-Fluoro-5-methoxybenzonitrile (0.62 g, 4.10 mmol), methanol (6.2 ml) and sodium hydroxide (6.2 ml, 6N aqueous). Stirred the resulting reaction mixture at 100°C overnight. Reaction mixture was cooled to room temperature and

concentrated *in-vacuo*. The residue was diluted with dichloromethane (100 ml) and acidified using hydrochloric acid (1N aqueous). The organic phase was separated, sequentially washed with water (100 ml) and brine (100 ml), dried (sodium sulfate) and concentrated *in-vacuo*, to yield the title compound (0.64g, 91%) as a white solid.

3-Cyano-5-thiomethylbenzoic acid

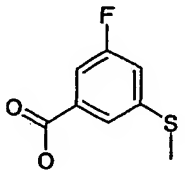


3-bromo-5-thiomethylbenzoic acid (519.6 mg, 2.1 mmol) was dissolved in diethyl ether (20 mL). Diazomethane in diethyl ether was added to the benzoic acid solution until the mixture ceased to bubble and a yellow colour persisted. Glacial acetic acid was added dropwise to this solution until the yellow colour disappeared. The reaction was washed with saturated sodium bicarbonate and brine, dried over anhydrous sodium sulfate and solvent was removed *in vacuo* to yield 537 mg (98%) of 3-bromo-5-thiomethylester as a colourless oil. 3-bromo-5-thiomethylester (536 mg, 2.05 mmol) was dissolved in anhydrous *N,N*-dimethylformamide (5 mL) in an argon atmosphere. Zinc cyanide (42 mg, 0.36 mmol) and tetrakis (triphenylphosphine) palladium(0) (41 mg, 0.356 mmol) was added to the reaction mixture, which was stirred at 80 °C for 10 hours. After cooling to room temperature, the reaction was diluted with water and extracted with ethyl acetate. The organic extracts were washed with brine, dried over anhydrous sodium sulfate and the solvent was removed *in vacuo*. The compound was purified by column chromatography on silica to yield 356 mg (85%) of 3-cyano-5-thiomethylester, which was a white solid.

3-cyano-5-thiomethylester (360 mg, 1.74 mol) was dissolved in anhydrous tetrahydrofuran (22 mL) and 21.6 mL of aqueous lithium hydroxide (0.5 M) and 11 mL of methanol was added. The reaction was refluxed for 45 minutes. The

reaction was cooled and the solvent was removed *in vacuo*. The mixture was diluted with water and washed with ethyl acetate. The aqueous layer was then acidified to pH 1 with HCl (1M) and extracted with ethyl acetate. The organic extractions were combined and dried over anhydrous sodium sulfate and solvent was removed *in vacuo* to give 330 mg (98%) of 3-cyano-5-thiomethylbenzoic acid as a white solid.

5-Fluoro-3-thiomethylbenzoic acid



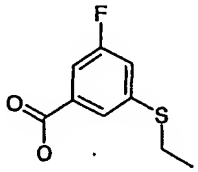
A solution of 3,5-difluorbromobenzene (1.0 g, 5.18 mmol) in *N,N*-dimethylformamide (15 mL) was cooled to 0 °C and sodiumthiomethoxide (363 mg, 5.18 mmol) was added. The reaction stirred for 30 minutes before the mixture was diluted with water and extracted with hexanes. The organic extracts were washed with brine and dried over anhydrous sodium sulphate. Solvent was removed *in vacuo* and the product was eluted through an SPE tube (10g) with hexanes to yield 618 mg (54%) of a colourless oil.

The 5-Fluoro-3-thiomethylbromobenzene (618 mg, 2.80 mmol) was dissolved in *N,N*-dimethylformamide (6 mL) and zinc cyanide (329 mg, 2.80 mmol) and tetrakis (triphenylphosphine)palladium (0) (324 mg, 0.28 mmol) were added to the solution. The reaction was stirred at 80 °C for 12 hours. The reaction mixture was cooled to R.T., diluted with water and extracted with ethyl acetate, washed with brine, dried over anhydrous sodium sulphate and the solvent was removed *in vacuo*. Silica gel chromatography using 5% ethyl acetate in hexanes afforded 430 mg (92%) of a white solid, 5-Fluoro-3-cyanothiomethylbenzene

(430 mg, 2.57 mmol) that was dissolved in water (6.0 ml) and aqueous sodium hydroxide (6M, 6.0 mL) and refluxed for 12 hours. The reaction mixture was acidified to pH 3 and extracted with ethyl acetate. The organic extracts were

washed with brine, dried over anhydrous sodium sulphate and the solvent was removed *in vacuo* to yield 470 mg (98%) of the title compound as a white solid.

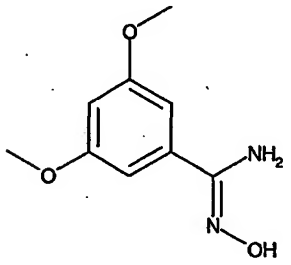
5-Fluoro-3-thioethylbenzoic acid



A solution of 3,5-difluorobromobenzene (1.0 g, 5.18 mmol) in *N,N*-dimethylformamide (15 mL) was cooled to 0 °C and sodiumthioethoxide (436 mg, 5.18 mmol) was added. The reaction stirred for 30 minutes before the mixture was diluted with water and extracted with hexanes. The organic extracts were washed with brine and dried over anhydrous sodium sulphate. Solvent was removed *in vacuo* and the product was eluted through an SPE tube (10g) with hexanes to yield 366 mg (30%) of a colourless oil,

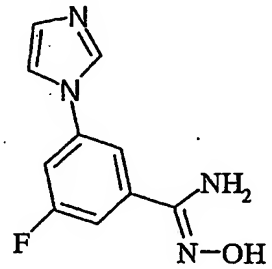
5-Fluoro-3-thioethylbromobenzene (365 mg, 1.55 mmol) that was dissolved in *N,N*-dimethylformamide (5 mL) and zinc cyanide (182 mg, 1.55 mmol) and tetrakis (triphenylphosphine)palladium (0) (179 mg, 0.16 mmol) were added to the solution. The reaction was stirred at 80 °C for 3 hours. The reaction mixture was cooled to R.T., diluted with water and extracted with ethyl acetate, washed with brine, dried over anhydrous sodium sulphate and solvent was removed *in vacuo*. Silica gel chromatography using 5% ethyl acetate in hexanes afforded 241mg (86%) of a white solid, 5-Fluoro-3-cyanothioethylbenzene (240 mg, 1.32 mmol) that was dissolved in water (3.0 ml) and aqueous sodium hydroxide (6M, 3.0 mL) and refluxed for 12 hours. The reaction mixture was acidified to pH 3 and extracted with ethyl acetate. The organic extracts were washed with brine, dried over anhydrous sodium sulphate and the solvent was removed *in vacuo* to yield 274 mg (103%) of an off-white solid.

3,5-dimethoxyphenylamidoxime



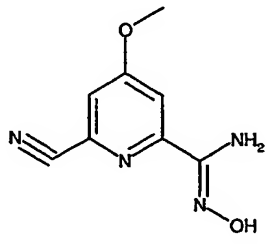
3,5-dimethoxybenzonitrile (228 mg, 1.4 mmol) and 5M hydroxylamine hydrochloride (0.336 mL, 1.68 mmol) in ethanol (2 mL) and 1 *N* sodium hydroxide (1.68 mL, 1.68 mmol), were heated at reflux overnight. Standard work up afforded 250 mg (91%) of 3,5-dimethoxyphenylamidoxime.

3-Fluoro-5-(1*H*-imidazol-1-yl)phenyl-amidoxime



3-Fluoro-5-(1*H*-imidazol-1-yl)benzonitrile (950 mg, 5.08 mmol) and 5M hydroxylamine hydrochloride (1.02 mL, 5.08 mmol) in ethanol (5 mL) and 1 *N* sodium hydroxide (5.08 mL, 5.08 mmol), were heated at reflux for 1 hour and 20 minutes. Standard work up afforded 901 mg (81.4%) of 3-bromo-5-fluorophenylamidoxime.

6-Cyano-4-methoxypyrid-2-yl-amidoxime



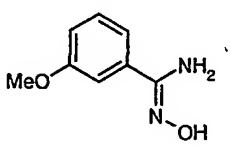
Chelidamic acid monohydrate (2.01 g, 10 mmol) was mixed with 1 M HCl (20 mL, 20 mmol, ether) in ethanol (50 mL) and heated at 85 °C for 24 hours. The solvent was removed *in vacuo* and mixed with ethyl acetate and water. The ethyl acetate layer was dried and concentrated. The residue was triturated with hexanes and ether to give 1.6 g (66%) diethyl 4-hydroxy-2,6-pyridinedicarboxylate.

To a suspension of 60% sodium hydride (0.351 g, 8.77 mmol) in dimethylformamide(7.5 mL), a solution of diethyl 4-hydroxy-2,6-pyridinedicarboxylate (1.4 g, 5.85 mmol) in dimethylformamide (9 mL) was added dropwise under argon at room temperature and the reaction mixture was stirred for 5 minutes. Iodomethane (1.245 g, 8.77 mmol) was added and the reaction was stirred at room temperature for 20 hours. The mixture was poured into water and extracted with dichloromethane. The dichloromethane layer was dried, concentrated to give 1.45 g (97.8%) diethyl 4-methoxy-2,6-pyridinedicarboxylate.

Diethyl 4-methoxy-2,6-pyridinedicarboxylate (1.45 g, 5.73 mmol) was stirred with concentrated ammonium (40 mL) at room temperature for 10 minutes. The precipitate was filtered to give 0.93 g (83%) of 4-methoxypyridine-2,6-dicarboxamide.

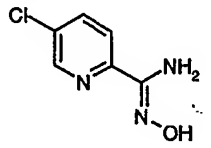
4-methoxypyridine-2,6-dicarboxamide (900 mg, 4.6 mmol) was mixed with trifluoroacetic anhydride (2.32 g, 11.1 mmol) and pyridine (1.6 g, 20.2 mmol) in dichloromethane (20 mL) and stirred overnight at room temperature. The reaction mixture was diluted with dichloromethane and washed with water. Standard work up, afforded 461 mg of 2,6-dicyano-4-methoxypyridine.2,6-Dicyano-4-methoxypyridine (460 mg, 2.89 mmol) and 5M hydroxylamine hydrochloride (0.578 mL, 2.89 mmol) in ethanol (3 mL) and 1 *N* sodium hydroxide (2.89 mL, 2.89 mmol), were stirred at room temperature overnight. Standard work up afforded 180 mg (32.4%) of 6-cyano-4-methoxypyrid-2-yl-amidoxime.

3-Methoxybenzamidoxime



Using the general procedure for the synthesis of amidoximes, hydroxylamine hydrochloride (7.65 g, 110 mmol), sodium hydroxide (11 mL of 10 *N*, 110 mmol), and 3-methoxybenzylnitrile (12.2 mL, 100 mmol) afforded 9.9 g (60%) of 3-methoxybenzamidoxime.

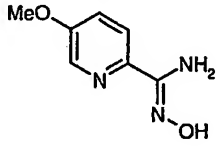
5-Chloropyrid-2-ylamidoxime



A mixture of 2,5-dichloropyridine (1.48 g, 10 mmol), zinc cyanide (705 mg, 6 mmol), zinc (dust, 29 mg, 0.45 mmol), [1,1'-bis(diphenylphosphino)ferrocene] dichloropalladium(II), complex with dichloromethane (1:1) (0.18 g, 0.22 mmol) in *N,N*-dimethylformamide (10 mL) was heated at reflux for 5 hours. After cooling, the reaction was diluted with ethyl acetate and extracted with water and brine. Silica gel chromatography afforded 735 mg (53%) of 2-cyano-5-chloropyridine.

Using the general procedure for the synthesis of amidoximes, 2-cyano-5-chloropyridine (735 mg, 5.3 mmol), a solution of hydroxylamine hydrochloride (1.2 mL of 5 M, 6 mmol) in ethanol (7 mL), and sodium hydroxide (0.61 mL of 10 *N*, 6.1 mmol), were heated at reflux for 24 hours. Standard work up afforded 707 mg (77%) of 5-chloropyrid-2-ylamidoxime.

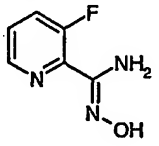
5-Methoxypyrid-2-ylamidoxime



A solution of 2-cyano-5-fluoropyridine (0.65 g, 5.3 mmol) in sodium methoxide (1.83 mL of 25% wt. solution in methanol, 7.95 mmol) was stirred at 0 °C for 1.5 hours and 2 hours at ambient temperature. The reaction was then diluted with ethyl acetate and washed with water and brine. Removal of the solvent *in vacuo* afforded 304 mg (43%) of 2-cyano-5-methoxypyridine.

Using the general procedure for the synthesis of amidoximes, 2-cyano-5-methoxypyridine (270 mg, 2.01 mmol), a solution of hydroxylamine hydrochloride (0.457 ml of 5 M, 2.28 mmol) in ethanol (4 mL), and sodium hydroxide (0.230 mL of 10 *N*, 2.30 mmol) were heated at reflux for 24 hours. Standard work up afforded 79 mg (24%) of 5-methoxypyrid-2-ylamidoxime.

3-Fluoropyrid-2-ylamidoxime

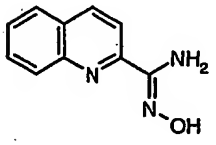


A mixture of 2,3-dichloropyridine (1.48 g, 10 mmol), zinc cyanide (705 mg, 6 mmol,), zinc (dust, 29 mg, 0.45 mmol), [1,1'-bis(diphenylphosphino)ferrocene] dichloropalladium(II), complex with dichloromethane (1:1) (0.18 g, 0.22 mol) in *N,N*-dimethylformamide (10 mL) was heated at reflux for 5 hours. After cooling, the reaction was diluted with ethyl acetate and extracted with water and brine. Removal of the solvent and silica gel chromatography afforded 1.05 g (76%) of 2-cyano-3-chloropyridine.

A solution of 2-cyano-3-chloropyridine (1 g, 7.22 mmol) in 1-methyl-2-pyrrolidinone (25 mL) was treated with potassium fluoride (1.26 g, 21.68 mmol) and heated at reflux for 18 hours. After cooling, the reaction was diluted with ethyl acetate and extracted with water and brine. Silica gel chromatography afforded 442 mg (50%) of 2-cyano-3-fluoropyridine.

Using the general procedure for the synthesis of amidoximes, 2-cyano-3-fluoropyridine (442 mg, 3.62 mmol), a solution of hydroxylamine hydrochloride (0.82 mL of 5 M, 4.1 mmol) in ethanol (5 mL), and sodium hydroxide (0.415 ml of 10 *N*, 4.15 mmol) were heated at reflux for 24 hours. Standard work up afforded 368 mg (66%) of 3-fluoropyrid-2-ylamidoxime.

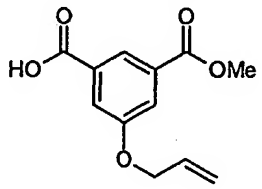
Quinol-2-ylamidoxime



Using the general procedure for the synthesis of amidoximes, 2-quinolinecarbonitrile (1.02 g, 6.6 mmol), a solution of hydroxylamine hydrochloride (1.44 mL of 5 *N* solution, 7.2 mmol) in ethanol (10 mL), and sodium hydroxide (0.72 mL of 10 *N* solution, 7.2 mmol) were heated at reflux for 18 hours. Standard work up afforded 990 mg (80%) of quinol-2-ylamidoxime.

EXAMPLE 2: Synthesis of Carboxylic Acid Intermediates

5-Allyloxy-3-(methoxycarbonyl)benzoic acid

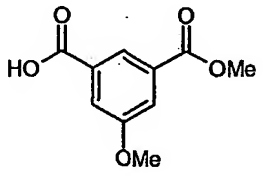


A stirred suspension of dimethyl 5-hydroxyisophthlate (5.0 g, 23.8 mmol) and potassium carbonate (7.5 g, 54.5 mmol) in acetone (120 mL) was treated with allyl bromide (4.6 mL, 53.0 mmol). The mixture was stirred at room temperature for 3 days. The mixture was then filtered and concentrated. The residue was dissolved in ethyl acetate and washed with water and brine. The remaining organic solution was dried over anhydrous sodium sulfate, filtered, and concentrated. Trituration with hexane afforded 5.0 g (84 %) of dimethyl 5-allyloxy-isophthalate

A mixture of dimethyl 5-allyloxy-isophthalate (3.7 g, 14.9 mmol) in methanol (75 mL) was treated with 1M sodium hydroxide (13.4 mL, 13.4 mmol) and the reaction stirred at room temperature for 16 hours. The mixture was concentrated under vacuum and the resulting residue was dissolved in water. The aqueous layer was washed with ethyl acetate (3 x), and then acidified (pH 1) by the addition of aqueous HCl. The aqueous solution was then extracted with ethyl acetate. The

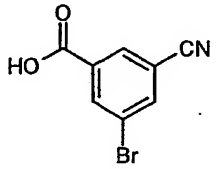
organic extract was dried over anhydrous sodium sulfate, filtered and concentrated to afford 2.6 g (74%) of 3-allyloxy-5-(methoxycarbonyl)benzoic acid.

3-Methoxycarbonyl-5-methoxybenzoic acid



In a similar fashion, dimethyl 5-hydroxyisophthlate (1.0 g, 4.8 mmol), potassium carbonate (1.5 mg, 10.9 mmol), and methyl iodide (0.7 mL, 10.6 mmol) in acetone (25 mL) afforded 1.1 g (99%) of dimethyl 5-methoxyisophthalate. Hydrolysis and standard work up afforded 0.7 g (68%) of 3-methoxycarbonyl-5-methoxybenzoic acid.

3-Bromo-5-cyanobenzoic acid



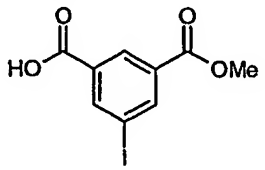
A mixture of 3-bromo-5-iodobenzoic acid (9.0 g) in methanol (40 mL) was treated with 1M HCl in diethyl ether (27.5 mL). The reaction was heated overnight at 40 °C. The solvent was then removed *in vacuo*, and the residue dissolved in ethyl acetate. The organic solution was washed with saturated sodium bicarbonate, dried over anhydrous sodium sulfate, filtered and concentrated to afford 8.8 g (94%) of methyl 3-bromo-5-iodobenzoate.

A solution of methyl 3-bromo-5-iodobenzoate (4.5 g, 13.2 mmol) in *N,N*-dimethylformamide (36 mL) was treated with zinc cyanide (1.7 g, 14.5 mmol) and tetrakis(triphenylphosphine)palladium(0) ($Pd(PPh_3)_4$, 1.5 g, 1.3 mmol). The reaction mixture was heated, under an argon atmosphere, for 1 hour at 80 °C. After cooling the mixture was diluted with ethyl acetate. The resulting organic solution was washed with water (3x), saturated brine, dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo*. Silica gel chromatography using a gradient of

hexane to 10% ethyl acetate in hexane afforded 1.9 g (61%) of methyl 3-bromo-5-cyanobenzoate.

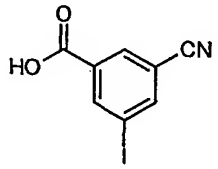
Hydrolysis of the methyl ester (1.9 g, 8.0 mmol) in methanol (20 mL) and 1M sodium hydroxide (8.0 mL, 8.0 mmol), afforded, after standard work up 1.6 g (88 %) of 3-bromo-5-cyanobenzoic acid.

3-Methoxycarbonyl-5-iodobenzoic acid



In a similar fashion, hydrolysis of dimethyl-5-iodoisophthlate (4.5 g, 14.058 mmol) in methanol (60 mL) with 1M NaOH (12.6 mL, 12.6 mmol) afforded, after standard work up 3.43 g (80%) of 3-methoxycarbonyl-5-iodobenzoic acid.

3-Cyano-5-iodobenzoic acid

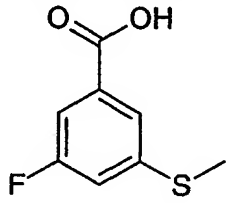


A solution of 3-methoxycarbonyl-5-iodobenzoic acid (3 g, 10 mmol) in thionyl chloride (2 mL) was heated for 2 hours at 60 °C. The reaction mixture was cooled and concentrated *in vacuo*. The intermediate acid chloride was then diluted with tetrahydrofuran (10 mL) and cooled to 0 °C. The mixture was then treated with a solution of 2M ammonia (20 mL, 40 mmol, methanol) and the reaction stirred for 1 hour at 0 °C. The mixture was then filtered and the solvent removed *in vacuo*. Recrystallization from methanol afforded 2.5 g (82%) of 3-methoxycarbonyl-5-iodobenzamide, as a white solid.

A mixture of 3-methoxycarbonyl-5-iodobenzamide (2.5 g, 8.2 mmol) in thionyl chloride (2 mL) was heated for 2 hours at 90 °C. The reaction mixture was cooled and concentrated *in vacuo*. Silica gel chromatography afforded 670 mg (29%) of methyl-3-cyano-5-iodobenzoate, as a white solid.

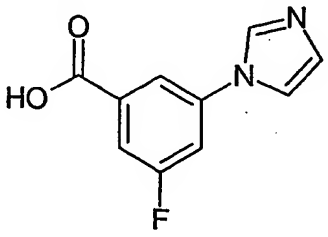
A solution of methyl-3-cyano-5-iodobenzoate (640 mg, 2.3 mmol) in tetrahydrofuran (8 mL) was treated with 0.5M LiOH (5.5 mL, 2.75 mmol) and methanol. The reaction mixture was heated at reflux for 1 hour. The solvent was concentrated *in vacuo* and the mixture treated with 1*N* HCl. The resulting white precipitate was filtered and the filtrate was extracted with dichloromethane. The residue and the extracted filtrate were combined and concentrated *in vacuo* to afford 590 mg (94%) of 3-cyano-5-iodobenzoic acid, as a white solid.

5-fluoro-3-(thiomethyl)benzoic acid



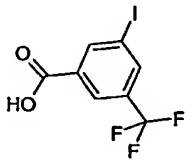
1-Bromo-3,5-difluorobenzene (1.00 g, 5.18 mmol) was dissolved in anhydrous DMF (10 mL). The solution was chilled in an ice bath, and NaSMe (0.36 g, 5.18 mmol) was added. After 30 minutes the reaction mixture was poured into water (100 mL) and extracted with hexanes. The organic phase was washed with water and brine, dried ($MgSO_4$), filtered, and concentrated to provide the title compound as a colourless oil. The crude product was used directly in the next step. Using the standard cyanation procedure, 5-cyano-3-fluoro-1-(thiomethyl)benzene was prepared as a yellow oil. The crude product was used directly in the next step. Using the standard saponification procedure, the title compound was prepared in 0.60 g yield (63% over 3 steps) as a colourless solid.

3-Fluoro-5-(1*H*-imidazol-1-yl)benzoic acid



1-Bromo-3,5-difluorobenzene (1.00 g, 5.18 mmol) was dissolved in anhydrous DMF (10 mL). The solution was chilled in an ice bath. Imidazole (0.36 g, 5.18 mmol) and K_2CO_3 (0.72 g, 5.18 mmol) were added. The reaction mixture was stirred at room temperature for 16 hours, and at 80 °C for 24 hours. The reaction mixture was poured into water (100 mL) and extracted with EtOAc. The organic phase was washed with brine, dried ($MgSO_4$), filtered, and concentrated. The intermediate 3-Fluoro-5-Bromo-(1H-imidazol-1-yl)-benzene was used directly in the next step. Using the standard cyanation procedure, 3-Fluoro-5-cyano-(1H-imidazol-1-yl)-benzene was prepared as a colourless solid. The crude product was used directly in the next step. Using the standard saponification procedure, the title compound was prepared as a colourless solid. The crude product was used directly in the next step.

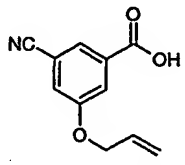
3-Iodo-5-Trifluoromethylbenzoic acid



The title product was prepared according to the literature procedure (Fujiki, Kanji; Kashiwagi, Mitsuyoshi; Miyamoto, Hideyuki; Sonoda, Akinari; Ichikawa, Junji; et al *J.Fluorine Chem.* **1992**, *57*, 307-321) from 3,5-bis(trifluoromethyl)benzene (7.3 mL, 47 mmol) and iodine (11.95 g, 47 mmol) in 30% oleum (30 mL) at 55 degrees for 15h. Quenching with ice was followed by extraction of the crude product into ether, sequential washing of the aqueous layer with sodium sulfite (1M) and water. Sodium hydroxide (!N, ~150 mL) was added to the crude ether solution until pH basic, the layers were separated and the aqueous layer was then acidified using HCl (12N, ~10 mL, pH acidic). Extraction into ether followed by drying over magnesium sulfate yielded the crude acid (4.3 g, 29%). The material was insufficiently pure for use, so the product was esterified using acetyl chloride in methanol, purified using flash chromatography (silica gel,

20% dichloromethane in hexane) and hydrolyzed with sodium hydroxide in methanol yielding 2.95 g (69%) of pure 3-iodo-5-Trifluoromethylbenzoic acid.

3-Allyloxy-5-cyanobenzoic acid



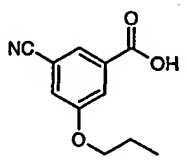
A suspension of 3-allyloxy-5-(methoxycarbonyl)benzoic acid (5.5 mg, 23 mmol) in thionyl chloride (30 mL) was heated at reflux for 2 hours. The excess thionyl chloride was then removed *in vacuo* and the intermediate acid chloride dissolved in dichloromethane (25 mL). After cooling to 0 °C the solution was treated with 0.5 M ammonia in 1,4-dioxane (100 mL) and then allowed to warm to room temperature. After 2 hours of stirring the solvent was removed *in vacuo* and the residue was titurated with water. The precipitate was collected, washed with water, and dried *in vacuo* to afford the 5.0 g (92 %) of methyl 3-(allyloxy)-(5-aminocarbonyl)benzoate as a white solid.

A suspension of methyl 3-(allyloxy)-(5-aminocarbonyl)benzoate (5.0 g, 21 mmol) in a dichloromethane (70 mL) at 0 °C was treated with pyridine (3.5 mL, 43 mmol) and then trifluoroacetic anhydride drop-wise (3.6 mL, 25 mmol). The reaction was stirred at 0 °C for 20 minutes and then stirred overnight at ambient temperature. The reaction mixture was washed with water and saturated brine, dried over anhydrous sodium sulfate, filtered and concentrated. Silica gel chromatography using a 10 % ethyl acetate/hexanes afforded 3.8 g (81%) of methyl 3-(allyloxy)-5-cyanobenzoate as a white solid.

A solution of methyl 3-(allyloxy)-5-cyanobenzoate (1.5 g, 6.9 mmol) in methanol-tetrahydrofuran (1:2, 30 mL) was treated with 0.5 N lithium hydroxide (17 mL, 8.3 mmol). The reaction was stirred at 70°C for 30 minutes and then the solvent was removed *in vacuo*. The residue was dissolved in a small amount of water and then acidified (pH ~ 4) by the addition of 2N hydrogen chloride. The

precipitate was collected and dried to afford 1.0 g (74%) of 3-allyloxy-5-cyanobenzoic acid as a white solid.

3-Cyano-5-propoxybenzoic acid



A suspension of 3-allyloxy-5-(methoxycarbonyl)benzoic acid (5.5 mg, 23 mmol) in thionyl chloride (30 mL) was heated at reflux for 2 hours. The excess thionyl chloride was then removed in vacuo and the intermediate acid chloride dissolved in dichloromethane (25 mL). After cooling to 0 °C the solution was treated with 0.5 M ammonia in 1,4-dioxane (100 mL) and then allowed to warm to room temperature. After 2 hours of stirring the solvent was removed in vacuo and the residue was titurated with water. The precipitate was collected, washed with water, and dried *in vacuo* to afford the 5.0 g (92 %) of methyl 3-(allyloxy)-(5-aminocarbonyl)benzoate as a white solid.

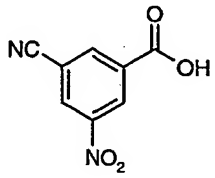
Methanol (20 mL) and dichloromethane (20 mL) were added to round bottom flask that contained methyl 3-(allyloxy)-(5-aminocarbonyl)benzoate (2.0 g, 8.5 mmol) and palladium(10 wt.% on activated carbon, 200 mg) under argon. The flask was evacuated using a water aspirator and then filled with hydrogen from a balloon. The balloon filled was hydrogen was attached to the flask as the reaction stirred for 2 hours. The palladium on carbon was remove by filtration through celite. The solvent was removed using a roto-evaporator and then the sample was dried under vacuum to afford 2.0 (97%) of methyl 3-(aminocarbonyl)-5-propoxybenzoate as a white solid.

A suspension of methyl 3-(aminocarbonyl)-5-propoxybenzoate (2.0 g, 8.2 mmol) in a dichloromethane (25 mL) at 0 °C was treated with pyridine (1.3 mL, 17 mmol) and then trifluoroacetic anhydride dropwise (1.4 mL, 9.9 mmol). The reaction was stirred at 0 °C for 20 minutes and then stirred overnight at ambient temperature. The reaction mixture was washed with water and saturated brine,

dried over anhydrous sodium sulfate, filtered and concentrated. Silica gel chromatography using a 40 % dichloromethane/hexanes afforded 1.5 g (84%) of methyl 3-cyano-5-propoxybenzoate as a white solid.

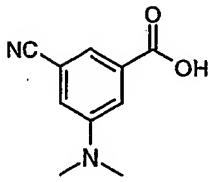
A solution of methyl 3-cyano-5-propoxybenzoate (1.5 g, 6.8 mmol) in methanol-tetrahydrofuran (1:2, 30 mL) was treated with 0.5 M lithium hydroxide (16 mL, 8.2 mmol). The reaction was stirred at 70°C for 30 minutes and then the solvent was removed *in vacuo*. The residue was dissolved in a small amount of water and then acidified (pH ~ 4) by the addition of 2*N* hydrogen chloride. The precipitate was collected and dried to afford 1.2 g (86%) of 3-cyano-5-propoxybenzoic acid.

3-Cyano-5-nitrobenzoic acid



Using the same procedure as for 3-allyloxy-5-cyanobenzoic acid, 3-cyano-5-nitrobenzoic acid (2.0 g, 10.7 mmol) was prepared from mono-methyl 5-nitroisophthalate (5.0 g, 22 mmol).

3-Cyano-5-dimethylaminobenzoic acid



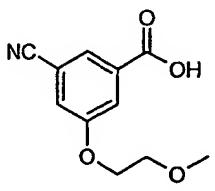
Methyl 3-cyano-2-nitrobenzoate (6.0g, 29 mmol) and tin(II) chloride dihydrate (26 g, 12 mmol) in methanol (100 mL) were heated at reflux for 3 hours. The reaction mixture was transferred into a 1L Erlenmeyer flask equipped with a stirring bar and containing ice. While stirring the reaction mixture, 1N sodium hydroxide was added until pH ~ 4-5. At this point solid sodium bicarbonate was

added until pH ~ 8. The mixture was transferred to a separatory funnel and extracted with ethyl acetate. The organic layer was washed with water and saturated brine, dried over anhydrous sodium sulfate, filtered and concentrated. Silica gel chromatography using 30 % ethyl acetate/hexanes afforded 2.4 g (47%) of methyl 3-amino-5-cyanobenzoate as a light brown solid.

Formaldehyde, 37 wt. % solution in water, (4.3 mL, 57 mmol), solid sodium cyanoborohydride (752 mg, 11 mmol), and then acetic acid (909 µL, 16 mmol) were added to methyl 3-amino-5-cyanobenzoate (500 mg, 2.8 mmol) in acetonitrile (10 mL). After stirring at ambient temperature for 5 hours, the reaction mixture was transferred to a separatory funnel and then ethyl acetate was added. The organic layer was washed with water and saturated brine, dried over anhydrous sodium sulfate, filtered, and concentrated. Silica gel chromatography using 15% ethyl acetate/hexanes afforded 390 mg (55%) methyl-3-cyano-5-dimethylaminobenzoate.

A solution of methyl-3-cyano-5-dimethylaminobenzoate (318 mg, 1.6 mmol) in tetrahydrofuran (5 mL) was treated with 0.5 N lithium hydroxide (3.7 mL, 1.9 mmol). The reaction was stirred at 70°C for 30 minutes and then the solvent was removed *in vacuo*. The residue was dissolved in a small amount of water and then acidified by the dropwise addition of 2 *N* hydrogen chloride until a white precipitate no longer formed. Following extraction of the aqueous layer with diethyl ether, the organic layer was then washed with water and saturated brine, dried over anhydrous sodium sulfate, filtered, and concentrated to afford 308 mg (quantitative) of 3-cyano-5-dimethylaminobenzoic acid.

3-cyano-5-(2-methoxyethoxy)benzoic acid



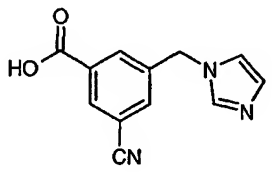
A mixture of methyl 3-allyloxy-5-cyanobenzoate (1.5 g, 6.9 mmol) and tetrabutylammonium iodide (2.8 g, 7.6 mmol) in dichloromethane (38 mL) at –78

°C, under argon, was treated with a solution of 1M boron trichloride in dichloromethane (24 mL, 24 mmol). After 5 minutes at –78 °C, the reaction mixture was stirred at ambient temperature for 1 hour. The reaction was then quenched with ice water and stirred for an additional 30 minutes. The organic layer was washed with saturated sodium bicarbonate, dried over anhydrous sodium sulfate, filtered and concentrated. Silica gel chromatography using a gradient of 20-30% ethyl acetate/hexanes afforded 811 mg (67%) of methyl 3-cyano-5-hydroxybenzoate as a light yellow solid.

A mixture of methyl 3-cyano-5-hydroxybenzoate (302 mg, 1.7 mmol), potassium carbonate (471 mg, 3.4 mmol) and 2-chloroethyl methyl ether (309 µL mg, 3.4 mmol) in *N,N*-dimethylformamide (4 mL) was heated in a sealed vial at 140 °C for 15 minutes. The reaction was cooled, diluted with ethyl acetate, washed with water and saturated brine, filtered and concentrated. Filtration through silica gel using dichloromethane afforded 375 mg (93%) of methyl 3-cyano-5-(2-methoxyethoxy)benzoate.

A solution of methyl 3-cyano-5-(2-methoxyethoxy)benzoate (375 mg, 1.6 mmol) in tetrahydrofuran (4 mL) was treated with 0.5 N lithium hydroxide (3.8 mL, 1.9 mmol). The reaction was stirred at 70°C for 30 minutes and then the solvent was removed *in vacuo*. The residue was dissolved in a small amount of water and then acidified with 2 *N* hydrogen chloride until pH ~ 2. Following extraction of the aqueous layer with ethyl acetate, the organic layer washed with water and saturated brine, dried over anhydrous sodium sulfate, filtered, and concentrated to afford 343 mg (97%) of 3-cyano-5-(2-methoxyethoxy)benzoic acid.

3-cyano-5-(1H-imidazol-1-yl-methyl)benzoic acid



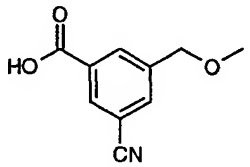
A mixture of methyl 3-(bromomethyl)-5-iodobenzoate (500 mg, 1.4 mmol), potassium carbonate (388 mg, 2.8 mmol), and imidazole (96 mg, 1.4 mmol) in

N,N-dimethylformamide (4 mL) was heated at 70 °C for 3 hours. After cooling, the reaction mixture was diluted with water and then extracted with dichloromethane. The organic layer was washed with water and saturated brine, dried over anhydrous sodium sulfate, filtered, and concentrated. Silica gel chromatography using 100% ethyl acetate afforded 242 mg (51%) of methyl 3-(imidazol-1-ylmethyl)-5-iodobenzoate as a white solid.

After bubbling argon into a solution of methyl 3-(imidazol-1-ylmethyl)-5-iodobenzoate (242 mg, 0.70 mmol) in N,N-dimethylformamide (2 mL) for 5 minutes, zinc cyanide (90 mg, 0.77 mmol) and tetrakis(triphenylphosphine)palladium(0) (80 mg, 0.070 mmol) were added. The reaction mixture was heated at 80°C for 30 minutes under argon. Following cooling, the reaction mixture was diluted with ethyl acetate and then the precipitate that formed was removed by filtration. The filtrate was washed with water and saturated brine, dried over anhydrous sodium sulfate, filtered, and concentrated. The residue was triturated with 20 % diethyl ether/hexanes, filtered, and dried in vacuo to afford 150 mg (89%) of 3-cyano-5-(1H-imidazol-1-yl-methyl)benzoate as a white solid.

A solution of 3-cyano-5-(1H-imidazol-1-yl-methyl)benzoate (150 mg, 0.62 mmol) in tetrahydrofuran (2 mL) was treated with 0.5 N lithium hydroxide (1.5 mL, 0.75 mmol). The reaction was stirred at 70°C for 10 minutes and then the solvent was removed *in vacuo*. The residue was dissolved in a small amount of water and then acidified (pH ~ 4) by the addition of 2*N* hydrogen chloride. The precipitate was collected and dried to afford 140 mg (quantitative) of 3-cyano-5-(1H-imidazol-1-yl-methyl)benzoic acid.

3-cyano-5-(methoxymethyl)benzoic acid

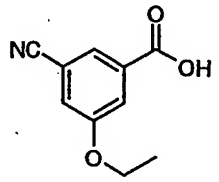


A mixture of methyl 3-(bromomethyl)-5-iodobenzoate (400 mg, 1.1 mmol) and potassium carbonate (311 mg, 2.3 mmol) in methanol/tetrathydrofuran (5 mL/5 mL) was heated at 55 °C for 1 hour. After cooling, the reaction mixture was diluted with water and then extracted with ethyl acetate. The organic layer was washed with water and saturated brine, dried over anhydrous sodium sulfate, filtered, and concentrated. After drying in vacuo, 325 mg (94%) of methyl 3-(methoxymethyl)-5-iodobenzoate was isolated as a white solid.

After bubbling argon into a solution of methyl 3-(methoxymethyl)-5-iodobenzoate (316 mg, 1.03 mmol) in N,N-dimethylformamide (3 mL) for 5 minutes, zinc cyanide (133 mg, 1.13 mmol) and tetrakis(triphenylphosphine)palladium(0) (119 mg, 0.010 mmol) were added. The reaction mixture was heated at 80°C for 15 minutes under argon. Following cooling, the reaction mixture was diluted with ethyl acetate and then the precipitate that formed was removed by filtration. The filtrate was washed with water and saturated brine, dried over anhydrous sodium sulfate, filtered, and concentrated. Silica gel chromatography using 10-30% ethyl acetate/hexanes afforded 184 mg (86%) of methyl 3-cyano-5-(methoxymethyl)benzoate as a colorless oil.

A solution of methyl 3-cyano-5-(methoxymethyl)benzoate (184 mg, 0.75 mmol) in tetrahydrofuran (2.1 mL) was treated with 0.5 N lithium hydroxide (1.8 mL, 0.90 mmol). The reaction was stirred at 70°C for 30 minutes and then after cooling the solvent was removed *in vacuo*. The residue was dissolved in a small amount of water and then acidified with 2 *N* hydrogen chloride until pH ~ 2-3. Following extraction of the aqueous layer with ethyl acetate, the organic layer washed with water and saturated brine, dried over anhydrous sodium sulfate, filtered, and concentrated to afford 145 mg (quantitative) of 3-cyano-5-(methoxymethyl)benzoic acid.

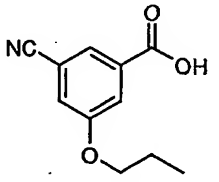
3-cyano-5-ethoxybenzoic acid



A solution of methyl 3-cyano-5-hydroxybenzoate (270 mg, 1.5 mmol) and potassium carbonate (482 mg, 3.4 mmol) in acetone (5.5 mL) was prepared. To this, ethyl iodide (272 µL, 3.4 mmol) was added and the reaction was heated at 52°C for 2.5 hours. The reaction mixture was concentrated, re-dissolved in ethyl acetate and washed with water and saturated brine. The organic solvent layer was collected, dried over anhydrous sodium sulphate, filtered, and concentrated. 321 mg (99%) of methyl 3-cyano-5-ethoxybenzoate was isolated as a light brown solid.

Methyl 3-cyano-5-ethoxybenzoate (312 mg, 1.5 mmol) was hydrolyzed as previously described to afford 290 mg (quantitative) of 3-cyano-5-ethoxybenzoic acid as an off-white solid.

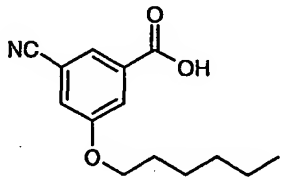
3-cyano-5-propoxybenzoic acid



A solution of methyl 3-cyano-5-hydroxybenzoate (200 mg, 1.3 mmol) and potassium carbonate (357 mg, 2.6 mmol) in acetone (4.0 mL) was prepared. To this, propyl iodide (245 µL, 2.5 mmol) was added and the reaction was heated at 50°C for 5 hours. The reaction mixture was concentrated, re-dissolved in ethyl acetate and washed with water and saturated brine. The organic solvent layer was collected, dried over anhydrous sodium sulphate, filtered, and concentrated. 222 mg (90%) of methyl 3-cyano-5-propoxybenzoate was isolated as a light brown solid.

Methyl 3-cyano-5-propoxybenzoate (222 mg, 1.0 mmol) was hydrolyzed as previously described to afford 169 mg (80%) of 3-cyano-5-propoxybenzoic acid as an off-white solid.

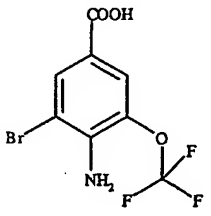
3-cyano-5-hexyloxybenzoic acid



A solution of methyl 3-cyano-5-hydroxybenzoate (170 mg, 0.95 mmol) and potassium carbonate (304 mg, 2.2 mmol) in acetone (4.0 mL) was prepared. To this, 1-bromohexane (300 µL, 2.1 mmol) was added and the reaction was heated at 50°C overnight. The reaction mixture was concentrated, re-dissolved in ethyl acetate and washed with water and saturated brine. The organic solvent layer was collected, dried over anhydrous sodium sulphate, filtered, and concentrated. Trituration with hexanes afforded 250 mg (quantitative) of methyl 3-cyano-5-hexyloxybenzoate as a light brown solid.

Methyl 3-cyano-5-ethoxybenzoate (250 mg, 0.95 mmol) was hydrolyzed as previously described to afford 247 mg (quantitative) of 3-cyano-5-hexyloxybenzoic acid as an off-white solid.

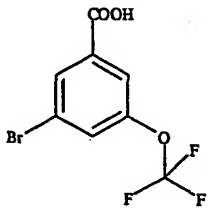
4-Amino-3-bromo-5-trifluoromethoxybenzoic acid



To a solution of 4-amino-3-trifluoromethoxybenzoic acid (5 g, 22.6 mmoles) in acetic acid (50 mL), bromine(3.98 g, 24.9 mmoles) in acetic acid(10 mL) was added dropwise at room temperature. After the reaction mixture was kept stirring for one hour, water was added into the mixture. The solid was filtered and washed

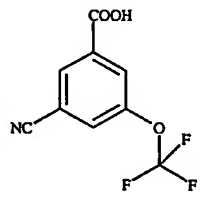
with water to give 4-amino-3-bromo-5-trifluoromethoxybenzoic acid (3.9 g, 54.9%).

3-Bromo-5-trifluoromethoxybenzoic acid



4-Amino-3-bromo-5-trifluoromethoxybenzoic acid (1.5 g, 5 mmoles) was mixed with ethanol (15 mL) at 0 °C and then concentrated sulfuric acid (2.26 g, 10.2 mmoles) wad added. The sodium nitrite (0.38 g, 5.5 mmoles) water solution (1.2 mL) was added dropwise at 0 °C for 1 hour. After the reaction mixture was warmed to room temperature and then heated to reflux for 45 minutes, water was added. The mixture was extracted with dichloromethane. The dichloromethane layer was dried and concentrated. The residue was dissolved in 1M sodium hydroxide and extracted with ether. The aqueous solution was acidified with 2M HCl to pH = 2 to give 3-bromo-5-trifluoromethoxybenzoic acid (1.08 g, 75.5%).

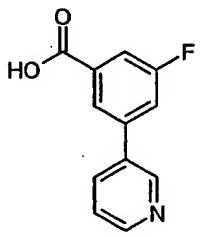
3-Cyano-5-trifluoromethoxybenzoic acid



To an ether solution of 3-bromo-5-trifluoromethoxybenzoic acid (1.08 g, 3.79 mmloes), tirmethylsilylmethyl azide was added in and stirred at room temperature for 10 minutes. The reaction was quenched with methanol and passed column with 2% ethyl acetate in hexanes to give colorless oil (0.84 g). This colorless oil was mixed with zinc cyanide (0.33 g, 2.8 mmoles) and tetrakis(triphenylphosphine)palladium(0) ($Pd(PPh_3)_4$, 467 mg, 0.404 mmol) in N,N-

dimethylformamide(10 mL) under argon at 85 °C overnight. The reaction mixture was diluted with dichloromethane and washed with water twice. The dichloromethane layer was dried and concentrated. The residue was mixed with1M sodium hydroxide (8 mL) and methanol (4 mL) and stirred at room temperature for 2 hours. The mixture was acidified with 1M HCl to pH = 1 ~ 2 and extracted with ethyl acetate. The ethyl acetate layer was washed with Brine and concentrated. The residue was passed column with 2% ethyl acetate in hexanes to give 3-cyano-5-trifluoromethoxybenzoic acid, which contained 3-[imino(methoxy)methyl]-5-trifluoromethoxybenzoic acid (3:1, 145 mg, 16.6%)

3-Fluoro-5-(3-pyridyl)benzoic acid



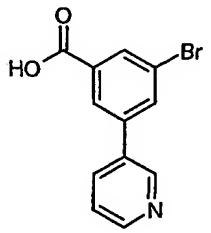
A solution of 3-Bromo-5-fluorobenzoic acid (2.00 g, 9.13 mmol) in thionyl chloride (16 ml) and dimethylformamide (0.4 ml) was stirred at 80°C for 1h. The reaction mixture was concentrated *in-vacuo* and the residue was dissolved in methanol (15 ml) and left stirring at room temperature overnight. The reaction mixture was concentrated *in-vacuo*, and the residue was dissolved in ethyl acetate (50 ml). Organic phase was sequentially washed with water (50 ml), saturated sodium bicarbonate (50 ml, aqueous), water (50 ml) and brine (50 ml), dried (sodium sulfate), filtered and concentrated *in-vacuo* to provide the title compound (1.97 g, 92%) as yellow oil.

To the solution of Methyl-3-bromo-5-fluorobenzoate (1.97 g, 8.44 mmol) in toluene (40 ml) added Pyridine-3-boronic acid-1,3-propanediol ester (1.79 g, 7.63 mmol), potassium carbonate (11.66 g, 84.4 mmol) and tetrakis(triphenylphoshine)palladium (0) (0.49, 0.42 mmol), sequentially. The resulting brownish yellow reaction mixture was heated at 120°C under argon overnight. The reaction mixture was cooled to room temperature, filtered through

a pad of celite and concentrated *in-vacuo*. The residue was purified on silica gel using 1% methanol in dichloromethane to isolate the title compound (0.92 g, 47%) as a yellow solid.

In a 100 ml round bottom flask equipped with stir bar added Methyl-3-fluoro-5-(3-pyridyl)benzoate (0.92 g, 3.93 mmol), methanol (10 ml) and sodium hydroxide (5.89 ml, 5.89 mmol, 1N aqueous). Stirred the resulting mixture at 50°C for 2 h. The reaction mixture was cooled to room temperature, concentrated *in-vacuo* and the residue was dissolved in methanol (20 ml). To this mixture added hydrochloric acid (1N diethyl ether) dropwise and stirred at room temperature for 10 min. The reaction mixture was concentrated *in-vacuo* and the residue was triturated with diethyl ether to provide the crude hydrochloride salt of title compound (1.00 g) as an off white solid.

3-Bromo-5-(3-pyridyl)benzoic acid



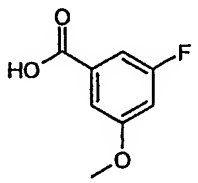
A solution of 3-Bromo-5-iodobenzoic acid (5.00 g, 15.3 mmol) in methanol (30 ml) and hydrochloric acid (15.3 ml, 15.3 mmol, 1N diethyl ether) was stirred at room temperature for 48h. The reaction mixture was concentrated *in-vacuo* and the residue was diluted with dichloromethane (100 ml). The organic phase was sequentially washed with sodium hydroxide (100 ml, 1N aqueous), water (100 ml) and brine (100 ml), dried (sodium sulfate), filtered and concentrated *in-vacuo*. The crude residue was dissolved in 10% ethyl acetate in hexanes (100 ml) and filtered through a pad of silica gel. Upon concentrating *in-vacuo*, isolated the methyl ester (4.98 g, 95%) as yellowish white solid.

To the solution of Methyl-3-bromo-5-iodobenzoate (2.00 g, 5.87 mmol) in toluene (50 ml) added Pyridine-3-boronic acid-1,3-propanediol ester (1.24 g, 7.63 mmol), potassium carbonate (8.11 g, 58.7 mmol) and

tetrakis(triphenylphoshine)palladium (0) (0.34, 0.29 mmol), sequentially. The resulting brownish yellow reaction mixture was heated at 80°C under argon for 10 h. The reaction mixture was cooled to room temperature, filtered through a pad of celite and concentrated *in-vacuo*. The residue was purified on silica gel using 3% methanol in dichloromethane to isolate Methyl-3-bromo-5-(3-pyridyl)benzoate (1.16 g, 67%) as a white solid.

In a 100 ml round bottom flask equipped with stir bar added Methyl-3-bromo-5-(3-pyridyl)benzoate (1.16 g, 3.96 mmol), methanol (15 ml) and sodium hydroxide (5.94 ml, 5.94 mmol, 1N aqueous). Stirred the resulting mixture at 50°C for 2 h. The reaction mixture was cooled to room temperature, concentrated *in-vacuo* and the residue was dissolved in methanol (20 ml). To this mixture added hydrochloric acid (1N diethyl ether) dropwise and stirred at room temperature for 10 min. The reaction mixture was concentrated *in-vacuo* and the residue was triturated with diethyl ether to provide the crude hydrochloride salt of title compound (1.50 g) as a white solid.

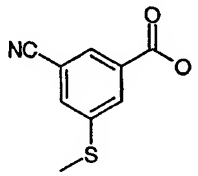
3-Fluoro-5-methoxybenzoic acid



In a 250 ml round bottom flask equipped with stir bar added 3,5-Difluorobenzonitrile (4.2 g, 30.4 mmol), sodium methoxide (10.4 ml, 45.6 mmol, 25% methanol) and dimethylformamide (40 ml). Stirred the resulting reaction mixture at room temperature, overnight. The reaction mixture was concentrated *in-vacuo* and residue was dissolved in dichloromethane (200 ml). The organic phase was washed sequentially with water (150 ml) and brine (150 ml), dried (sodium sulfate) and concentrated *in-vacuo*. The crude residue was purified on silica gel using 10% diethyl ether in hexanes to isolate 3-Fluoro-5-methoxybenzonitrile (1.63 g) as a white solid.

In a 50 ml round bottom flask equipped with stir bar and reflux condensor added 3-Fluoro-5-methoxybenzonitrile (0.62 g, 4.10 mmol), methanol (6.2 ml) and sodium hydroxide (6.2 ml, 6N aqueous). Stirred the resulting reaction mixture at 100°C overnight. Reaction mixture was cooled to room temperature and concentrated *in-vacuo*. The residue was diluted with dichloromethane (100 ml) and acidified using hydrochloric acid (1N aqueous). The organic phase was separated, sequentially washed with water (100 ml) and brine (100 ml), dried (sodium sulfate) and concentrated *in-vacuo*, to yield the title compound (0.64g, 91%) as a white solid.

3-Cyano-5-thiomethylbenzoic acid

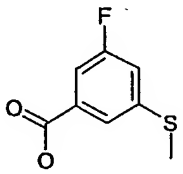


3-bromo-5-thiomethylbenzoic acid (519.6 mg, 2.1 mmol) was dissolved in diethyl ether (20 mL). Diazomethane in diethyl ether was added to the benzoic acid solution until the mixture ceased to bubble and a yellow colour persisted. Glacial acetic acid was added dropwise to this solution until the yellow colour disappeared. The reaction was washed with saturated sodium bicarbonate and brine, dried over anhydrous sodium sulfate and solvent was removed *in vacuo* to yield 537 mg (98%) of 3-bromo-5-thiomethylester as a colourless oil. 3-bromo-5-thiomethylester (536 mg, 2.05 mmol) was dissolved in anhydrous *N,N*-dimethylformamide (5 mL) in an argon atmosphere. Zinc cyanide (42 mg, 0.36 mmol) and tetrakis (triphenylphosphine) palladium(0) (41 mg, 0.356 mmol) was added to the reaction mixture, which was stirred at 80 °C for 10 hours. After cooling to room temperature, the reaction was diluted with water and extracted with ethyl acetate. The organic extracts were washed with brine, dried over anhydrous sodium sulfate and the solvent was removed *in vacuo*. The compound

was purified by column chromatography on silica to yield 356 mg (85%) of 3-cyano-5-thiomethylester, which was a white solid.

3-cyano-5-thiomethylester (360 mg, 1.74 mol) was dissolved in anhydrous tetrahydrofuran (22 mL) and 21.6 mL of aqueous lithium hydroxide (0.5 M) and 11 mL of methanol was added. The reaction was refluxed for 45 minutes. The reaction was cooled and the solvent was removed *in vacuo*. The mixture was diluted with water and washed with ethyl acetate. The aqueous layer was then acidified to pH 1 with HCl (1M) and extracted with ethyl acetate. The organic extractions were combined and dried over anhydrous sodium sulfate and solvent was removed *in vacuo* to give 330 mg (98%) of 3-cyano-5-thiomethylbenzoic acid as a white solid.

5-Fluoro-3-thiomethylbenzoic acid



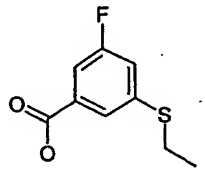
A solution of 3,5-difluorbromobenzene (1.0 g, 5.18 mmol) in *N,N*-dimethylformamide (15 mL) was cooled to 0 °C and sodiumthiomethoxide (363 mg, 5.18 mmol) was added. The reaction stirred for 30 minutes before the mixture was diluted with water and extracted with hexanes. The organic extracts were washed with brine and dried over anhydrous sodium sulphate. Solvent was removed *in vacuo* and the product was eluted through an SPE tube (10g) with hexanes to yield 618 mg (54%) of a colourless oil.

The 5-Fluoro-3-thiomethylbromobenzene (618 mg, 2.80 mmol) was dissolved in *N,N*-dimethylformamide (6 mL) and zinc cyanide (329 mg, 2.80 mmol) and tetrakis (triphenylphosphine)palladium (0) (324 mg, 0.28 mmol) were added to the solution. The reaction was stirred at 80 °C for 12 hours. The reaction mixture was cooled to R.T., diluted with water and extracted with ethyl acetate, washed with brine, dried over anhydrous sodium sulphate and the solvent was removed *in*

vacuo. Silica gel chromatography using 5% ethyl acetate in hexanes afforded 430 mg (92%) of a white solid, 5-Fluoro-3-cyanothiomethylbenzene

(430 mg, 2.57 mmol) that was dissolved in water (6.0 ml) and aqueous sodium hydroxide (6M, 6.0 mL) and refluxed for 12 hours. The reaction mixture was acidified to pH 3 and extracted with ethyl acetate. The organic extracts were washed with brine, dried over anhydrous sodium sulphate and the solvent was removed *in vacuo* to yield 470 mg (98%) of the title compound as a white solid.

5-Fluoro-3-thioethylbenzoic acid

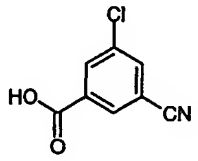


A solution of 3,5-difluorobromobenzene (1.0 g, 5.18 mmol) in *N,N*-dimethylformamide (15 mL) was cooled to 0 °C and sodiumthioethoxide (436 mg, 5.18 mmol) was added. The reaction stirred for 30 minutes before the mixture was diluted with water and extracted with hexanes. The organic extracts were washed with brine and dried over anhydrous sodium sulphate. Solvent was removed *in vacuo* and the product was eluted through an SPE tube (10g) with hexanes to yield 366 mg (30%) of a colourless oil,

5-Fluoro-3-thioethylbromobenzene (365 mg, 1.55 mmol) that was dissolved in *N,N*-dimethylformamide (5 mL) and zinc cyanide (182 mg, 1.55 mmol) and tetrakis (triphenylphosphine)palladium (0) (179 mg, 0.16 mmol) were added to the solution. The reaction was stirred at 80 °C for 3 hours. The reaction mixture was cooled to R.T., diluted with water and extracted with ethyl acetate, washed with brine, dried over anhydrous sodium sulphate and solvent was removed *in vacuo*. Silica gel chromatography using 5% ethyl acetate in hexanes afforded 241mg (86%) of a white solid, 5-Fluoro-3-cyanothioethylbenzene (240 mg, 1.32 mmol) that was dissolved in water (3.0 ml) and aqueous sodium hydroxide (6M, 3.0 mL) and refluxed for 12 hours. The reaction mixture was acidified to pH 3 and extracted with ethyl acetate. The organic extracts were washed with brine, dried

over anhydrous sodium sulphate and the solvent was removed *in vacuo* to yield 274 mg (103%) of an off-white solid.

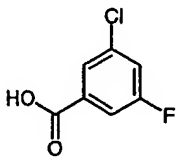
3-Chloro-5-cyanobenzoic acid



A mixture of methyl 3,5-dichlorobenzoate (14.66 g, 71.5 mmol), zinc cyanide (5.04 g, 42.9 mmol) zinc (dust, 0.21 g, 3.21mmol), [1,1'Bis(diphenylphosphino)ferrocene] dichloropalladium(II), complex with dichloromethane (1:1) (1.3 g, 1.57 mmol) in *N,N*-dimethylformamide (70 mL) was heated at reflux for 5 hours. After cooling the reaction was diluted with ethyl acetate and extracted with water and brine. Silica gel chromatography afforded 2.34g (17%) methyl 2-chloro-5-cyanobenzoate.

The intermediate ester was treated with a solution of sodium hydroxide (7.5 mL of 4 *N* solution, 30 mmol) in methanol (50 mL) and stirred at ambient temperature for18 hours. The solvent was removed *in vacuo* and the residue dissolved in ethyl acetate. The organic solution was washed with 5% HCl and brine. Removal of the solvent afforded 1.8 g (83%) of 3-chloro-5-cyanobenzoic acid.

3-Chloro-5-fluorobenzoic acid

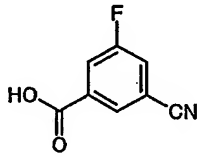


A mixture of 1-bromo-3-chloro-5-fluorobenzene (25.0 g, 120 mmol), zinc cyanide (8.45 g, 72 mmol) zinc (dust, 235 mg, 3.6 mmol), [1,1'Bis(diphenylphosphino)ferrocene] dichloropalladium(II), complex with dichloromethane (1:1) (1.5 g, 1.8 mmol) in *N,N*-dimethylformamide (70 ml) was heated at reflux for 1 hour. After cooling the reaction was diluted with ethyl

acetate and extracted with water and brine. Silica gel chromatography afforded 15.9g (85%) 3-chloro-5-fluorobenzonitrile.

The intermediate nitrile was treated with a solution of sodium hydroxide (100 mL of 10 *N* solution, 1 mol) in 100 mL water and heated at reflux for 2 hours. After this time the solution was cooled and acidified with concentrated hydrochloric acid. Extraction with dichloromethane and evaporation of the solvent, afforded 15.14g (85%) of 3-chloro-5-fluorobenzoic acid.

3-Fluoro-5-cyanobenzoic acid



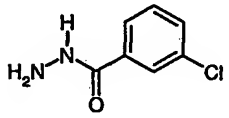
3-Chloro-5-fluorobenzoic acid (13.74g, 78.7 mmol) was treated with 50 ml thionyl chloride and heated at reflux for 2 hours. The excess thionyl chloride was removed *in vacuo* and the residue treated with 100 ml dry methanol to afford 13.6g (92%) of methyl 3-chloro-5-fluorobenzoate.

A mixture of the methyl 3-chloro-5-fluorobenzoate, zinc cyanide (8.46g, 72.3 mmol) zinc (dust, 235 mg, 3.6mmol), [1,1'bis(diphenylphosphino)ferrocene] dichloropalladium(II), complex with dichloromethane (1:1) (1.5 g, 1.8 mmol) in *N,N*-dimethylformamide (70 ml) was heated at reflux for 1 hour. The reaction was cooled to ambient temperature and diluted with ethyl acetate. The organic solution was extracted with water and brine and concentrated *in vacuo*, to afford crude methyl 3-chloro-5-cyanobenzoate.

The crude methyl 3-chloro-5-cyanobenzoate was treated with a solution of sodium hydroxide (45 ml of 4 *N* solution, 180 mmol) in methanol (350 mL) at ambient temperature for 4 hours. The solvent was removed *in vacuo* and the residue dissolved in ethyl acetate. The organic solution was washed with 5% aqueous HCl and brine. Silica gel chromatography afforded 7.0 g (54%) of 3-fluoro-5-cyanobenzoic acid.

EXAMPLE 3: Synthesis of 3-Chlorobenzhydrazide for Triazole Syntheses

3-Chlorobenzhydrazide

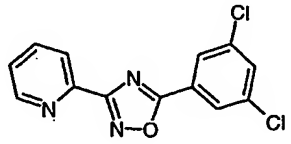


A mixture of 3-chlorobenzoic acid (0.5 g, 3.19 mmol), 1,3-diccyclohexylcarbodiimide (0.72 g, 3.51 mmol), 4-dimethylaminopyridine (0.04 g, 0.32 mmol) in ethanol was stirred at ambient temperature for 1.5 hour. The white solid was filtered off and the filtrate diluted with dichloromethane (100 mL). The organic solution was washed with 1 *N* sodium hydrogen sulfate (100 mL), saturated sodium bicarbonate (100 mL), water (100 mL) and brine (100 mL). The organic phase was dried over anhydrous magnesium sulfate and filtered. The filtrate was concentrated *in vacuo*. The crude residue was dissolved in ethanol (15 mL) and treated with hydrazine monohydrate (0.46 mL, 9.58 mmol). The resulting clear solution was stirred overnight at ambient temperature. The reaction mixture was then concentrated to dryness *in vacuo*. Silica gel chromatography of the residue, using 3% methanol in dichloromethane, afforded 0.29 g (53%) of 3-chlorobenzhydrazide as a white solid.

EXAMPLE 4

3-(2-Pyridyl)-5-(3,5-dichlorophenyl)-1,2,4-oxadiazole

B2

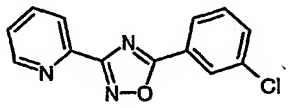


A mixture of 3,5-dichlorobenzoyl chloride (2.1 g, 10 mmol) and pyrid-2-ylamidoxime (1.37 g, 10 mmol) in pyridine (5 mL) was heated in sealed tube at 190 °C for 2 hours. After this time, the reaction mixture was added to ice cold water to precipitate the oxadiazole. The solid was collected by filtration, washed with water and then recrystallized from ethanol to yield 2.1 g (72%) of 3-(2-

pyridyl)-5-(3,5-dichlorophenyl)-1,2,4-oxadiazole: mp 162-166 °C; GC/EI-MS gave *m/z* (rel. int.) 291 (M^+, 38), 293 (25), 261 (1), 173 (6), 145 (13), 120 (100), 90 (20), 78 (28), 51 (15).

3-(2-Pyridyl)-5-(3-chlorophenyl)-1,2,4-oxadiazole

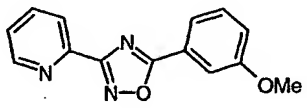
B3



Using the general procedure for the synthesis of 1,2,4-oxadiazoles, 3-chlorobenzoyl chloride (127 μL, 1 mmol) and pyrid-2-ylamidoxime (137 mg, 1 mmol) in pyridine (1 mL) were heated at reflux for 4 hours. Standard work up afforded 156 mg (61%) of 3-(2-pyridyl)-5-(3-chlorophenyl)-1,2,4-oxadiazole: mp 136-140 °C; GC/EI-MS gave *m/z* (rel. int.) 257 (M^+, 64), 259 (21), 227 (3), 120 (100), 111 (22), 90 (24), 78 (32), 75 (26), 51 (20).

3-(2-Pyridyl)-5-(3-methoxyphenyl)-1,2,4-oxadiazole

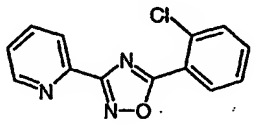
B1



Using the general procedure for the synthesis of 1,2,4-oxadiazoles, 3-anisoyl chloride (151 μL, 1 mmol) and pyrid-2-ylamidoxime (137 mg, 1 mmol) in pyridine (1 mL) were heated at reflux for 4 hours. Standard work up afforded 200 mg (79%) of 3-(2-pyridyl)-5-(3-methoxyphenyl)-1,2,4-oxadiazole: mp 96-99 °C; GC/EI-MS gave *m/z* (rel. int.) 253 (M^+, 100), 223 (3), 179 (3), 135 (74), 133 (90), 92 (27), 78 (29), 77 (32), 64 (23), 63 (23).

3-(2-Pyridyl)-5-(2-chlorophenyl)-1,2,4-oxadiazole

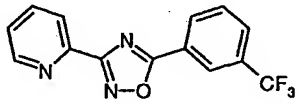
B5



Using the general procedure for the synthesis of 1,2,4-oxadiazoles, 2-chlorobenzoyl chloride (127 μL, 1 mmol) and pyrid-2-ylamidoxime (137 mg, 1 mmol) in pyridine (1 mL) were heated at reflux for 4 hours. Standard work up afforded 157 mg (61%) of 3-(2-pyridyl)-5-(2-chlorophenyl)-1,2,4-oxadiazole: mp 93-94 °C; GC/EI-MS gave *m/z* (rel. int.) 257 (M^+, 76), 259 (26), 227 (4), 139 (11), 120 (100), 111 (21), 90 (27), 78 (35), 75 (29), 51 (21).

3-(2-Pyridyl)-5-[3-(trifluoromethyl)phenyl]-1,2,4-oxadiazole

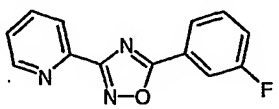
B6



Using the general procedure for the synthesis of 1,2,4-oxadiazoles, 3-(trifluoromethyl)benzoyl chloride (151 μL, 1 mmol) and pyrid-2-ylamidoxime (137 mg, 1 mmol) in pyridine (1 mL) were heated at reflux for 16 hours. Standard work up afforded 233 mg (80%) of 3-(2-pyridyl)-5-[3-(trifluoromethyl)phenyl]-1,2,4-oxadiazole: mp 116-118 °C; GC/EI-MS gave *m/z* (rel. int.) 291 (M^+, 81), 272 (7), 173 (6), 145 (25), 120 (100), 90 (20), 78 (23), 51 (11).

3-(2-Pyridyl)-5-(3-fluorophenyl)-1,2,4-oxadiazole

B7

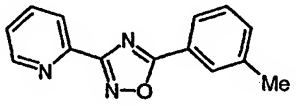


Using the general procedure for the synthesis of 1,2,4-oxadiazoles, 3-fluorobenzoyl chloride (122 μL, 1 mmol) and pyrid-2-ylamidoxime (137 mg, 1

mmol) in pyridine (1 mL) were heated at reflux for 16 hours. Standard work up afforded 176 mg (73%) of 3-(2-pyridyl)-5-(3-fluorophenyl)-1,2,4-oxadiazole: mp 88-98 °C; GC/EI-MS gave *m/z* (rel. int.) 241 (M^+, 95), 211 (5), 120 (100), 107 (13), 95 (30), 90 (21), 78 (27), 75 (19), 51 (15).

3-(2-Pyridyl)-5-(3-methylphenyl)-1,2,4-oxadiazole

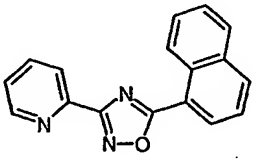
B9



Using the general procedure for the synthesis of 1,2,4-oxadiazoles, 3-toluoyl chloride (264 μL, 2 mmol) and pyrid-2-ylamidoxime (274 mg, 2 mmol) in pyridine (1 mL) were heated in a sealed tube at 200 °C for 2 hours. Standard work up afforded 387 mg (82%) of 3-(2-pyridyl)-5-(3-toluoyl)-1,2,4-oxadiazole: mp 127-128 °C; GC/EI-MS gave *m/z* (rel. int.) 237 (M^+, 100), 222 (2), 207 (8), 120 (68), 117 (24), 91 (29), 90 (29), 78 (32), 65 (26), 51 (23).

3-(2-Pyridyl)-5-(1-naphthyl)-1,2,4-oxadiazole

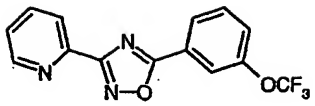
B10



Using the general procedure for the synthesis of 1,2,4-oxadiazoles, 1-naphthoyl chloride (150 μL, 1 mmol) and pyrid-2-ylamidoxime (137 mg, 1 mmol) in pyridine (1 mL) were heated in a sealed tube at 200 °C for 3 hours. Standard work up afforded 50 mg (18%) of 3-(2-pyridyl)-5-(1-naphthyl)-1,2,4-oxadiazole: mp 132-136 °C; GC/EI-MS gave *m/z* (rel. int.) 273 (M^+, 75), 195 (5), 169 (88), 153 (100), 139 (12), 127 (66), 126 (29), 105 (23), 78 (14), 51 (14).

3-(2-Pyridyl)-5-[3-(trifluoromethoxy)phenyl]-1,2,4-oxadiazole

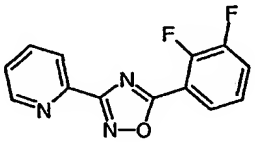
B11



Using the general procedure for the synthesis of 1,2,4-oxadiazoles, 3-(trifluoromethoxy)benzoyl chloride (220 mg, 1 mmol), and pyrid-2-ylamidoxime (137 mg, 1 mmol) in pyridine (1 mL) were heated in a sealed tube at 200 °C for 3 hours. Standard work up afforded 175 mg (57%) of 3-(2-pyridyl)-5-[3-(trifluoromethoxy)phenyl]-1,2,4-oxadiazole: mp 86-88 °C; GC/EI-MS gave *m/z* (rel. int.) 307 (M^+, 73), 277 (3), 222 (3), 189 (6), 161 (5), 120 (100), 78 (21), 69 (17), 51 (10).

3-(2-Pyridyl)-5-(2,3-difluorophenyl)-1,2,4-oxadiazole

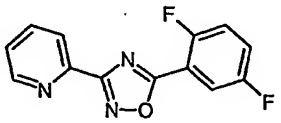
B16



Using the general procedure for the synthesis of 1,2,4-oxadiazoles, 2,3-difluorobenzoyl chloride (124 μL, 1 mmol) and pyrid-2-ylamidoxime (137 mg, 1 mmol) in pyridine (1 mL) were heated at 100 °C for 16 hours. Standard work up afforded 158 mg (61%) of 3-(2-pyridyl)-5-(2,3-difluorophenyl)-1,2,4-oxadiazole: mp 120-121 °C; GC/EI-MS gave *m/z* (rel. int) 259 (M^+, 97), 229 (5), 228 (4), 141 (11), 120 (100), 113 (26), 90 (27), 78 (34), 51 (17).

3-(2-Pyridyl)-5-(2,5-difluorophenyl)-1,2,4-oxadiazole

B17

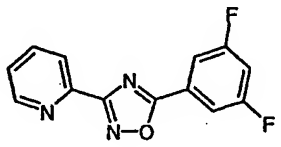


Using the general procedure for the synthesis of 1,2,4-oxadiazoles, 2,5-difluorobenzoyl chloride (124 μL, 1 mmol) and pyrid-2-ylamidoxime (137 mg, 1 mmol) in pyridine (1 mL) were heated at 100 °C for 16 hours. Standard work up

afforded 3-(2-pyridyl)-5-(2,5-difluorophenyl)-1,2,4-oxadiazole: mp 120-126 °C; GC/EI-MS gave *m/z* (rel. int) 259 (M^+, 91), 229 (5), 228 (4), 141 (13), 120 (100), 113 (25), 90 (23), 78 (27), 51 (14).

3-(2-Pyridyl)-5-(3,5-difluorophenyl)-1,2,4-oxadiazole

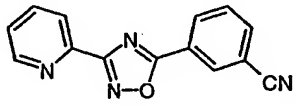
B18



Using the general procedure for the synthesis of 1,2,4-oxadiazoles, 3,5-difluorobenzoyl chloride (1.25 mL, 10 mmol) and pyrid-2-ylamidoxime (1.37 g, 10 mmol) in pyridine (5 mL) were heated in a sealed tube at 200 °C for 4 hours. Standard work up afforded 1.2 g (46%) of 3-(2-pyridyl)-5-(3,5-difluorophenyl)-1,2,4-oxadiazole: mp 115-119 °C; GC/EI-MS gave *m/z* (rel. int) 259 (M^+, 100), 229 (4), 228 (5), 141 (9), 125 (13), 113 (30), 90 (19), 78 (27), 63 (23), 51 (15).

3-(2-Pyridyl)-5-(3-cyanophenyl)-1,2,4-oxadiazole

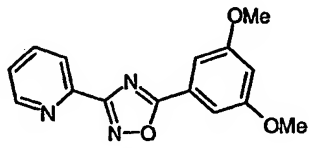
B21



Using the general procedure for the synthesis of 1,2,4-oxadiazoles, 3-cyanobenzoyl chloride (165 mg, 1 mmol) and pyrid-2-ylamidoxime (137 mg, 1 mmol) in pyridine (1 mL) were heated at 100 °C for 72 hours. Standard work up afforded 158 mg (64%) of 3-(2-pyridyl)-5-(3-cyanophenyl)-1,2,4-oxadiazole: mp 148-149 °C; GC/EI-MS gave *m/z* (rel. int.) 248 (M^+, 85), 218 (5), 130 (6), 120 (100), 114 (9), 102 (28), 90 (26), 78 (37), 75 (19), 51 (30).

3-(2-Pyridyl)-5-(3,5-dimethoxyphenyl)-1,2,4-oxadiazole

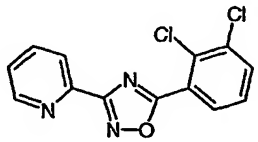
B23



Using the general procedure for the synthesis of 1,2,4-oxadiazoles, 3,5-dimethoxybenzoyl chloride (200 mg, 1 mmol) and pyrid-2-ylamidoxime (137 mg, 1 mmol) in pyridine (1 mL) were heated at 100 °C for 72 hours. Standard work up afforded 210 mg (74%) of 3-(2-pyridyl)-5-(3,5-dimethoxyphenyl)-1,2,4-oxadiazole: mp 145-148 °C; GC/EI-MS gave *m/z* (rel. int.) 283 (M^+, 100), 253 (3), 165 (69), 163 (19), 137 (36), 122 (33), 107 (17), 90 (10), 78 (25), 63 (19), 51 (19).

3-(2-Pyridyl)-5-(2,3-dichlorophenyl)-1,2,4-oxadiazole

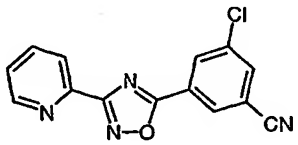
B25



Using the general procedure for the synthesis of 1,2,4-oxadiazoles, 2,3-dichlorobenzoyl chloride (209 mg, 1 mmol) and pyrid-2-ylamidoxime (137 mg, 1 mmol) in pyridine (1 mL) were heated at 100 °C for 48 hours. Standard work up afforded 236 mg (81%) of 3-(2-pyridyl)-5-(2,3-dichlorophenyl)-1,2,4-oxadiazole: mp 128-133 °C; GC/EI-MS gave *m/z* (rel. int.) 291 (M^+, 66), 293 (43), 256 (6), 173 (10), 145 (11), 120 (100), 90 (19), 78 (27), 51 (14).

3-(2-Pyridyl)-5-(3-chloro-5-cyanophenyl)-1,2,4-oxadiazole

B26

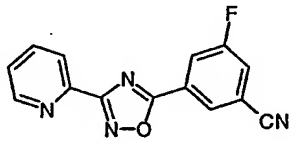


3-Chloro-5-cyanobenzoic acid (0.82 g, 4.97 mmol) was treated with a solution of oxalyl chloride (10 mL of 2.5 M in dichloromethane, 25 mmol) and a catalytic amount of *N,N*-dimethylformamide. The reaction was stirred at ambient temperature for 2.5 hours. The excess oxalyl chloride was removed *in vacuo* to afford 3-chloro-5-cyanobenzoyl chloride.

Using the general procedure for the synthesis of 1,2,4-oxadiazoles, the 3-chloro-5-cyanobenzoyl chloride and pyrid-2-ylamidoxime (682 mg, 5 mmol, 1 equivalent) in pyridine (5 mL) were heated in a sealed tube at 175 °C for 4 hours. Standard work up and recrystallization from 2-propanol afforded 250 mg (19%) of 3-(2-pyridyl)-5-(3-chloro-5-cyanophenyl)-1,2,4-oxadiazole: GC/EI-MS gave *m/z* (rel. int.) 282 (M^+, 100), 283 (18), 284 (34), 251 (4), 136 (10), 120 (53), 100 (10), 78 (15), 51 (6).

3-(2-Pyridyl)-5-(3-fluoro-5-cyanophenyl)-1,2,4-oxadiazole

B27

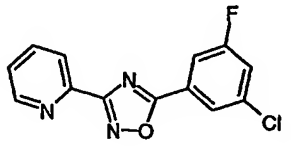


3-Fluoro-5-cyanobenzoic acid (2.5 g, 15.14 mmol) was treated with a solution of oxalyl chloride (30 mL of 2.5 M in dichloromethane, 75 mmol) and a catalytic amount of *N,N*-dimethylformamide. The reaction was stirred at ambient temperature for 2.5 hours. The excess oxalyl chloride was removed *in vacuo* to afford 3-fluoro-5-cyanobenzoyl chloride.

Using the general procedure for the synthesis of 1,2,4-oxadiazoles, the 3-fluoro-5-cyanobenzoyl chloride and pyrid-2-ylamidoxime (2.076 g, 15.15 mmol, 1 equivalent) in pyridine (5 mL) were heated in a sealed tube at 175 °C for 4 hours. Standard work up and recrystallization from 2-propanol afforded 1.5 g (37%) of 3-(2-pyridyl)-5-(3-fluoro-5-cyanophenyl)-1,2,4-oxadiazole: GC/EI-MS gave *m/z* (rel. int.) 266 (M^+, 81), 267 (13), 235 (5), 132 (12), 120 (100), 100 (18), 90 (18), 78 (35), 51 (20).

3-(2-Pyridyl)-5-(3-chloro-5-fluorophenyl)-1,2,4-oxadiazole

B28

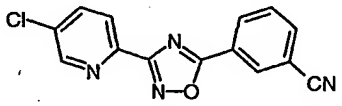


3-Chloro-5-fluorobenzoic acid (400 mg, 2.3 mmol) was treated with a solution of oxalyl chloride (4.6 mL of 2.5 M in dichloromethane, 11.5 mmol) and a catalytic amount of *N,N*-dimethylformamide. The reaction was stirred at ambient temperature for 2.5 hours. The excess oxalyl chloride was removed *in vacuo* to afford 3-chloro-5-fluorobenzoyl chloride.

Using the general procedure for the synthesis of 1,2,4-oxadiazoles, the 3-chloro-5-fluorobenzoyl chloride and pyrid-2-ylamidoxime (314 mg, 2.3 mmol, 1 equivalent) in pyridine (5 mL) were heated in a sealed tube at 175 °C for 4 hours. Standard work up and recrystallization from 2-propanol afforded 250 mg (39%) of 3-(2-pyridyl)-5-(3-chloro-5-fluorophenyl)-1,2,4-oxadiazole: GC/EI-MS gave *m/z* (rel. int.) 275(M^+, 89), 276 (14), 277 (29), 129 (26), 120 (100), 109 (7), 90 (20), 78 (31), 51 (14).

3-(5-Chloropyrid-2-yl)-5-(3-cyanophenyl)-1,2,4-oxadiazole

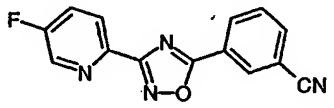
B29



Using the general procedure for the synthesis of 1,2,4-oxadiazoles, 3-cyanobenzoyl chloride (675 mg, 4mmol) and 5-chloropyrid-2-ylamidoxime (686 mg, 4 mmol) in pyridine (5 mL) were heated in a sealed tube at 175 °C for 4 hours. Standard work up and recrystallization from 2-propanol afforded 357 mg (32%) of 3-(5-chloropyrid-2-yl)-5-(3-cyanophenyl)-1,2,4-oxadiazole: GC/EI-MS gave *m/z* (rel. int.) 282 (M^+, 85), 283 (14), 284 (27), 156 (31), 154 (100), 112 (19), 102 (30), 76 (28), 64 (13).

3-(5-Fluoropyrid-2-yl)-5-(3-cyanophenyl)-1,2,4-oxadiazole

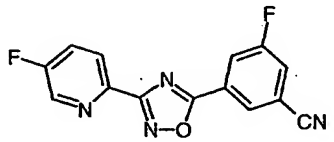
B30



Using the general procedure for the synthesis of 1,2,4-oxadiazoles, 3-cyanobenzoyl chloride (0.534 g, 3.2 mmol) and 5-fluoropyrid-2-ylamidoxime (0.5 g, 3.2 mmol) in pyridine (5 mL) were heated in a sealed tube at 175 °C for 4 hours. Standard work up and recrystallization from 2-propanol afforded 370 mg (43%) of 3-(5-fluoropyrid-2-yl)-5-(3-cyanophenyl)-1,2,4-oxadiazole: GC/EI-MS gave *m/z* (rel. int.) 266 (M^+, 100), 267 (10), 138 (80), 114 (8), 102 (19), 96 (22), 76 (17), 57 (8).

3-(5-Fluoropyrid-2-yl)-5-(3-cyano-5-fluorophenyl)-1,2,4-oxadiazole

B31

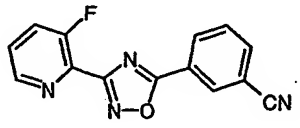


3-Fluoro-5-cyanobenzoic acid (1.0 g, 6 mmol) was treated with a solution of oxalyl chloride (12 mL of 2.5 M in dichloromethane, 30 mmol) and a catalytic amount of *N,N*-dimethylformamide. The reaction was stirred at ambient temperature for 2.5 hours. The excess oxalyl chloride was removed *in vacuo* to afford 3-fluoro-5-cyanbenzoyl chloride.

Using the general procedure for the synthesis of 1,2,4-oxadiazoles, the 3-fluoro-5-cyanbenzoyl chloride (1.1 g, 6 mmol) and 5-fluoropyrid-2-ylamidoxime (0.93 g, 6 mmol) in pyridine (5 mL) were heated in a sealed tube at 175 °C for 4 hours. Standard work up and recrystallization from 2-propanol afforded 0.41 g (24%) of 3-(5-fluoropyrid-2-yl)-5-(3-cyano-5-fluorophenyl)-1,2,4-oxadiazole: GC/EI-MS gave *m/z* (rel. int.) 284 (M^+, 100), 285 (16), 253 (2), 138 (99), 120 (23), 108 (16), 96 (25), 82 (15), 57 (11).

3-(3-Fluoropyrid-2-yl)-5-(3-cyanophenyl)-1,2,4-oxadiazole

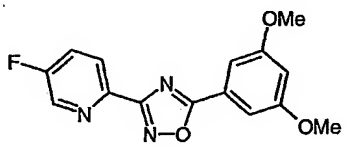
B32



Using the general procedure for the synthesis of 1,2,4-oxadiazoles, 3-cyanobenzoyl chloride (107 mg, 0.64 mmol) and 3-fluoropyrid-2-ylamidoxime (0.1 g, 0.64 mmol) in pyridine (5 mL) were heated in a sealed tube at 175 °C for 4 hours. Standard work up, silica gel chromatography, and recrystallization from 2-propanol, afforded 32 mg (19%) of 3-(3-fluoropyrid-2-yl)-5-(3-cyanophenyl)-1,2,4-oxadiazole: GC/EI-MS gave *m/z* (rel. int.) 266 (M^+, 75), 267 (12), 138 (100), 114 (11), 102 (19), 96 (17), 76 (16), 57 (5), 51 (5).

3-(5-Fluoropyrid-2-yl)-5-(3,5-dimethoxyphenyl)-1,2,4-oxadiazole

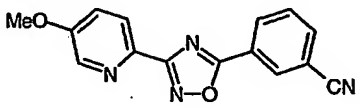
B33



Using the general procedure for the synthesis of 1,2,4-oxadiazoles, 3,5-dimethoxybenzoyl chloride (0.10 g, 0.5 mmol) and 5-fluoropyrid-2-ylamidoxime (78 mg, 0.5 mmol) in pyridine (3 mL) were heated in a sealed tube at 175 °C for 4 hours. Standard work up, silica gel chromatography, and recrystallization from 2-propanol afforded 94 mg (62%) of 3-(5-fluoropyrid-2-yl)-5-(3,5-dimethoxyphenyl)-1,2,4-oxadiazole: GC/EI-MS gave *m/z* (rel. int.) 301 (M^+, 100), 302 (17), 165 (41), 137 (23), 122 (27), 96 (15), 77 (11), 63 (12).

3-(5-Methoxypyrid-2-yl)-5-(3-cyanophenyl)-1,2,4-oxadiazole

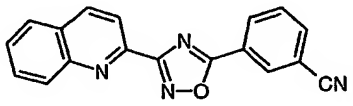
B34



Using the general procedure for the synthesis of 1,2,4-oxadiazoles, 3-cyanobenzoyl chloride (79 mg, 0.47 mmol) and 5-methoxypyrid-2-ylamidoxime (79 mg, 0.47 mmol) in pyridine (2.5 mL) were heated in a sealed tube at 175 °C for 4 hours. Standard work up, silica gel chromatography, and recrystallization from 2-propanol afforded 59 mg (45%) of 3-(5-methoxypyrid-2-yl)-5-(3-cyanophenyl)-1,2,4-oxadiazole: GC/EI-MS gave *m/z* (rel. int.) 278 (M^+, 100), 279 (16), 150 (56), 128 (7), 107 (21), 102 (17), 80 (12), 64 (5).

3-(2-Quinolinyl)-5-(3-cyanophenyl)-1,2,4-oxadiazole

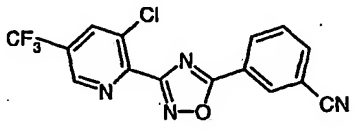
B35



Using the general procedure for the synthesis of 1,2,4-oxadiazoles, 3-cyanobenzoyl chloride (68 mg, 0.41 mmol) and quinol-2-ylamidoxime (75.9 mg, 0.405 mmol) in pyridine (0.5 mL) were heated in a sealed tube at 165 °C for 22 hours. Standard work up, recrystallization from ethanol, and solid phase extraction (SPE) afforded 23.7 mg (20%) of 3-(2-quinolinyl)-5-(3-cyanophenyl)-1,2,4-oxadiazole. ^{1}H-NMR ($CDCl_3$), δ (ppm): 8.62 (s, 1H), 8.54 (d, 1H), 8.36 (d, 2H), 8.28 (d, 1H), 7.90 (d, 2H), 7.80 (t, 1H), 7.72 (t, 1H), 7.64 (t, 1H).

3-(3-chloro-5-trifluoromethylpyrid-2-yl)-5-(3-cyanophenyl)-1,2,4-oxadiazole

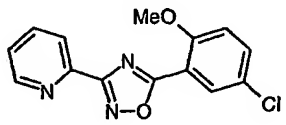
B36



Using the general procedure for the synthesis of 1,2,4-oxadiazoles, 3-cyanobenzoyl chloride (66 mg, 0.40 mmol) and 3-chloro-5-trifluoromethylpyrid-2-ylamidoxime (96.5 mg, 0.403 mmol) in pyridine (0.5 mL) were heated in a sealed tube at 165 °C for 22 hours. Standard work up and solid phase extraction (SPE) afforded 45.9 mg (33%) of 3-(3-chloro-5-trifluoromethylpyrid-2-yl)-5-(3-cyanophenyl)-1,2,4-oxadiazole. ^{1}H-NMR ($CDCl_3$), δ (ppm): 8.99 (s, 1H), 8.57 (s, 1H), 8.49 (d, 1H), 8.19 (s, 1H), 7.92 (d, 1H), 7.72 (t, 1H).

3-(2-pyridyl)-5-(5-chloro-2-methoxyphenyl)-1,2,4-oxadiazole

B37

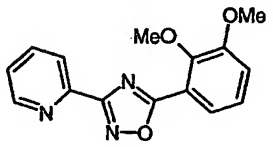


5-Chloro-*O*-anisic acid (187 mg, 1 mmol) was treated with a solution of oxalyl chloride (1.5 mL of 2 M in dichloromethane, 3 mmol) and a catalytic amount of *N,N*-dimethylformamide. The reaction was stirred at ambient temperature for 2 hours. The excess oxalyl chloride was removed *in vacuo* to afford 5-chloro-2-methoxybenzoyl chloride.

Using the general procedure for the synthesis of 1,2,4-oxadiazoles, the 5-chloro-2-methoxybenzoyl chloride and pyrid-2-ylamidoxime (137 mg, 1 mmol) in pyridine (1 mL) were heated at 115 °C for 17 hours. Standard work up, and silica gel chromatography afforded 49 mg (17%) of 3-(2-pyridyl)-5-(5-chloro-2-methoxyphenyl)-1,2,4-oxadiazole. ^{1}H-NMR ($CDCl_3$), δ (ppm): 4.00(s, 3H), 7.03 (d, J= 8.9 Hz, 1H), 7.42-7.47 (m, 1H), 7.50 (dd, J=8.9 Hz, 2.8 Hz, 1H), 7.87 (ddd, J= 1.4 Hz, 7.4 Hz, 8.2 Hz, 1H), 8.22 (d, J= 8.2 Hz, 1H), 8.28 (d, J = 2.4 Hz, 1H), 8.84 (m, 1H).

3-(2-pyridyl)-5-(2,3-dimethoxyphenyl)-1,2,4-oxadiazole

B38

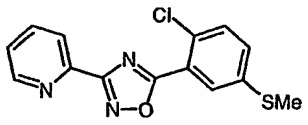


2,3-Dimethoxybenzoic acid (182 mg, 1 mmol) was treated with a solution of oxalyl chloride (1.5 mL of 2 M in dichloromethane, 3 mmol) and a catalytic amount of *N,N*-dimethylformamide. The reaction was stirred at ambient temperature for 2 hours. The excess oxalyl chloride was removed *in vacuo* to afford 2,3-dimethoxybenzoyl chloride.

Using the general procedure for the synthesis of 1,2,4-oxadiazoles, the 2,3-dimethoxybenzoyl chloride and pyrid-2-ylamidoxime (137 mg, 1 mmol) in pyridine (1 mL) were heated at 115 °C for 17 hours. Standard work up and silica gel chromatography afforded 120 mg (42%) of 3-(2-pyridyl)-5-(2,3-dimethoxyxyphenyl)-1,2,4-oxadiazole.

3-(2-pyridyl)-5-(2-chloro-5-methylthiophenyl)-1,2,4-oxadiazole

B39



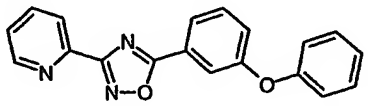
2-Chloro-5-methylthiobenzoic acid (182 mg, 1 mmol) was treated with a solution of oxalyl chloride (1.5 mL of 2 M in dichloromethane, 3 mmol) and a catalytic amount of *N,N*-dimethylformamide. The reaction was stirred at ambient temperature for 2 hours. The excess oxalyl chloride was removed *in vacuo* to afford 2-chloro-5-methylthiobenzoyl chloride.

Using the general procedure for the synthesis of 1,2,4-oxadiazoles, the 2-chloro-5-methylthiobenzoyl chloride and pyrid-2-ylamidoxime (137 mg, 1 mmol) in pyridine (1 mL) were heated at 115 °C for 17 hours. Standard work up and silica gel chromatography afforded 250 mg (82%) of 3-(2-pyridyl)-5-(2-chloro-5-

methylthiophenyl)-1,2,4-oxadiazole. ^{1}H-NMR ($CDCl_3$), δ (ppm): 7.37(dd, J= 2.4Hz, 8.2 Hz, 1H), 7.40-7.50 (m, 2H), 7.89 (ddd, J= 1.4 Hz, 7.4 Hz, 8.2 Hz, 1H), 8.05 (d, J=2.4 Hz, 1H), 8.23 (dd, J=2.2 Hz, 8.0 Hz, 1 x H), 8.85 (m, 1H).

3-(2-Pyridyl)-5-(3-phenoxyphenyl)-1,2,4-oxadiazole

B40

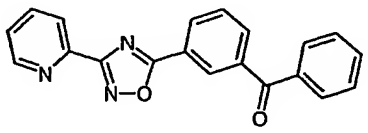


3-Phenoxybenzoic acid (214 mg, 1.0 mmol) was treated with a solution of oxalyl chloride (1.5 mL of 2 M in dichloromethane, 3 mmol) and a catalytic amount of *N,N*-dimethylformamide. The reaction was stirred overnight at ambient temperature. The excess oxalyl chloride was removed *in vacuo* to afford 3-phenoxybenzoyl chloride.

Using the general procedure for the synthesis of 1,2,4-oxadiazoles, the 3-phenoxybenzoyl chloride and pyrid-2-ylamidoxime (137 mg, 1 mmol) in pyridine (1 mL) were heated in a sealed vial overnight at 110 °C. Standard work up afforded 118 mg (37%) of 3-(2-pyridyl)-5-(3-phenoxyphenyl)-1,2,4-oxadiazole as a white solid.

3-(2-Pyridyl)-5-(3-benzoylphenyl)-1,2,4-oxadiazole

B41

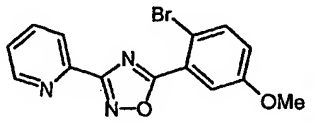


3-Benzoylbenzoic acid (226 mg, 1.0 mmol) in dichloromethane (1.5 mL) was treated with a solution of oxalyl chloride (1.5 mL of 2 M in dichloromethane, 3 mmol) and a catalytic amount of *N,N*-dimethylformamide. The reaction was stirred overnight at ambient temperature. The excess oxalyl chloride was removed *in vacuo* to afford 3-benzoylbenzoyl chloride.

Using the general procedure for the synthesis of 1,2,4-oxadiazoles, the 3-benzoylbenzoyl chloride and pyrid-2-ylamidoxime (137 mg, 1 mmol) in pyridine (1 mL) were heated in a sealed vial overnight at 110 °C. Standard work up and filtration through silica gel (with dichloromethane) afforded 200 mg (61%) of 3-(2-pyridyl)-5-(3-benzoylphenyl)-1,2,4-oxadiazole as a white solid. ^{1}H NMR ($CDCl_3$), δ (ppm): 8.85 (d, 1H), 8.68 (m, 1H), 8.53 (dd, 1H), 8.23 (d, 1H), 8.07 (m, 1H), 7.88 (m, 3H), 7.70 (m, 2H), 7.49 (m, 3H).

3-(2-Pyridyl)-5-(2-bromo-5-methoxyphenyl)-1,2,4-oxadiazole

B42

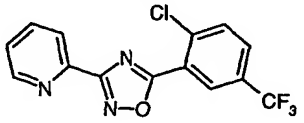


2-Bromo-5-methoxybenzoic acid (231 mg, 1.0 mmol) in dichloromethane (1.5 mL) was treated with a solution of oxalyl chloride (1.5 mL of 2 M in dichloromethane, 3 mmol) and a catalytic amount of *N,N*-dimethylformamide. The reaction was stirred overnight at ambient temperature. The excess oxalyl chloride was removed *in vacuo* to afford 2-bromo-5-methoxybenzoyl chloride.

Using the general procedure for the synthesis of 1,2,4-oxadiazoles, the 2-bromo-5-methoxybenzoyl chloride and pyrid-2-ylamidoxime (137 mg, 1 mmol) in pyridine (1 mL) were heated in a sealed vial overnight at 110 °C. Standard work up and filtration through silica gel (with dichloromethane) afforded 147 mg (44%) of 3-(2-pyridyl)-5-(2-bromo-5-methoxyphenyl)-1,2,4-oxadiazole. ^{1}H NMR ($CDCl_3$), δ (ppm): 8.85 (d, 1H), 8.24 (d, 1H), 7.89 (m, 1H), 7.65 (m, 2H), 7.47 (m, 1H), 6.99 (m, 1H), 3.89 (s, 3H).

3-(2-Pyridyl)-5-(2-chloro-5-(trifluoromethyl)phenyl)-1,2,4-oxadiazole

B43

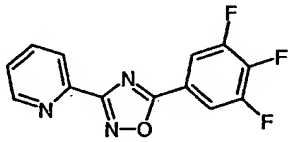


2-Chloro-5-(trifluoromethyl)benzoic acid (224 mg, 1.0 mmol) in dichloromethane (1.5 mL) was treated with a solution of oxalyl chloride (1.5 mL of 2 M in dichloromethane, 3 mmol) and a catalytic amount of *N,N*-dimethylformamide. The reaction was stirred overnight at ambient temperature. The excess oxalyl chloride was removed *in vacuo* to afford 2-chloro-5-(trifluoromethyl)benzoyl chloride.

Using the general procedure for the synthesis of 1,2,4-oxadiazoles, the 2-chloro-5-(trifluoromethyl)benzoyl chloride and pyrid-2-ylamidoxime (137 mg, 1 mmol) in pyridine (1 mL) were heated in a sealed vial overnight at 110 °C. Standard work up and filtration through silica gel (with dichloromethane) afforded 136 mg (42%) of 3-(2-pyridyl)-5-(2-chloro-5-(trifluoromethyl)phenyl)-1,2,4-oxadiazole as a beige solid. ^{1}H NMR ($CDCl_3$), δ (ppm): 8.87 (d, 1H), 8.56 (s, 1H), 8.25 (d, 1H), 7.89 (m, 1H), 7.78 (m, 2H), 7.50 (m, 1H).

3-(2-Pyridyl)-5-(3,4,5-trifluorophenyl)-1,2,4-oxadiazole

B44

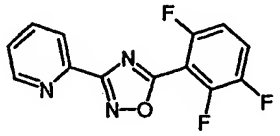


3,4,5-Trifluorobenzoic acid (0.176 g, 1.0 mmol) in dichloromethane (1.5 mL) was treated with a solution of oxalyl chloride (1.5 mL of 2 M in dichloromethane, 3 mmol) and a catalytic amount of *N,N*-dimethylformamide. The reaction was stirred overnight at ambient temperature. The excess oxalyl chloride was removed *in vacuo* to afford 3,4,5-trifluorobenzoyl chloride.

Using the general procedure for the synthesis of 1,2,4-oxadiazoles, the 3,4,5-trifluorobenzoyl chloride and pyrid-2-ylamidoxime (137 mg, 1 mmol) in pyridine (1 mL) were heated in a sealed vial overnight at 110 °C. Standard work up and silica gel chromatography (with 10-30% ethyl acetate in hexane) afforded 15 mg (5%) of 3-(2-pyridyl)-5-(3,4,5-trifluorophenyl)-1,2,4-oxadiazole as a white solid.

3-(2-pyridyl)-5-(2,5,6-trifluorophenyl)-1,2,4-oxadiazole

B45



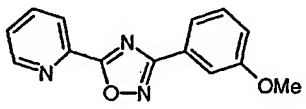
2,5,6-Trifluorolbenzoic acid (176 mg, 1 mmol) was treated with a solution of oxalyl chloride (1.5 mL of 2 M in dichloromethane, 3 mmol) and a catalytic amount of *N,N*-dimethylformamide. The reaction was stirred at ambient temperature for 16 hours. The excess oxalyl chloride was removed *in vacuo* to afford 2,5,6-trifluorolbenzoyl chloride.

A solution of the intermediate 2,5,6-trifluorolbenzoyl chloride and pyrid-2-ylamidoxime (137 mg, 1 mmol) in dichloromethane was stirred at ambient temperature for 0.5 hours. Silica gel chromatography afforded 151 mg (51%) of *N*-[(2,5,6-trifluorobenzoyl) oxy]pyridine-2-carboximidamide.

A solution of *N*-[(2,5,6- trifluorobenzoyl)oxy]pyridine-2-carboximidamide (50 mg, 0.169 mmol) in pyridine (0.3 mL) was heated at 115 °C for 17 hours. Standard work up, and silica gel chromatography, afforded 9.5 mg (20%) of 3-(2-pyridyl)-5-(2,5,6-trifluorophenyl)-1,2,4-oxadiazole.

3-(3-Methoxyphenyl)-5-(2-pyridyl)-1,2,4-oxadiazole

B8

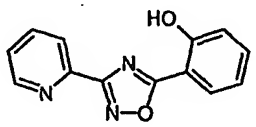


Using modifications of the method of Shine et al., *J. Heterocyclic Chem.* (1989) *26*:125-128, a solution of picolinic acid (123 mg, 1 mmol) in pyridine (1 mL) was treated with 1,1'-carbonyldiimidazole (162 mg, 1 mmol) and the reaction stirred at ambient temperature until the evolution of carbon dioxide ceased (30 min). The intermediate acylimidazole was then treated with 3-methoxybenzamidoxime (166 mg, 1 mmol) and the reaction heated at reflux for 1 hour. Ice cold water was added to the reaction mixture to precipitate the

oxadiazole. The solid was collected by filtration, washed with water and dried to afford 80 mg (32%) of 3-(3-methoxyphenyl)-5-(2-pyridyl)-1,2,4-oxadiazole: mp 90-94 °C; GC/EI-MS gave *m/z* (rel. int.) 253 (M^+, 100), 254 (17), 179 (2), 175 (2), 149 (77), 133 (33), 119 (4), 106 (29), 78 (45), 51 (18).

3-(Pyrid-2-yl)-5-(2-hydroxyphenyl)-1,2,4-oxadiazole

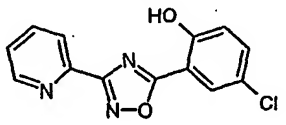
B46



Using the method of Korbonits et al., *J. Chem. Soc. Perkin Trans. I* (1982) 759-766, a mixture of ethyl salicylate (200 mg, 1.2 mmol), pyrid-2-ylamidoxime (82.5 mg, 0.6 mmol), 21% sodium ethoxide (19.4 mL, 6 mmol) in ethanol (12mL) was heated at reflux for 16 hours. After cooling, the reaction mixture was diluted with dichloromethane (50 mL) and washed with water and saturated sodium hydrocarbonate. The organic layer was dried with sodium sulfate and concentrated *in vacuo*. Recrystallization from diethyl ether afforded 15 mg (5%) of 3-(Pyrid-2-yl)-5-(2-hydroxyphenyl)-1,2,4-oxadiazole.

3-(2-pyridyl)-5-(5-chloro-2-hydroxyphenyl)-1,2,4-oxadiazole

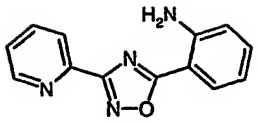
B47



In a similar fashion, methyl 5-chloro-2-hydroxybenzoate (372 mg, 2 mmol), pyrid-2-ylamidoxime (137 mg, 1 mmol), 21 % sodium ethoxide (32.4 mL, 10 mmol) in ethanol (20 mL) were heated at reflux for 16 hours. Standard work up and recrystallization from diethyl ether afforded 14.2 mg (5%) of 3-(2-pyridyl)-5-(5-chloro-2-hydroxyphenyl)-1,2,4-oxadiazole.

3-(2-pyridyl)-5-(2-aminophenyl)-1,2,4-oxadiazole

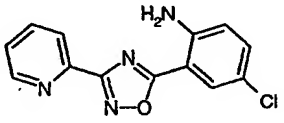
B48



Using modifications from the procedure of Nagahara et al., *Chem. Pharm. Bull.*, (1975) *23*:3178-3183, a mixture of isatoic anhydride (163 mg, 1 mmol) and pyrid-2-ylamidoxime (137 mg, 1 mmol) in pyridine (1 mL) was heated at 115 °C for 17 hours. After cooling the reaction, the mixture was diluted with 50 mL of dichloromethane and washed with water and saturated sodium hydrocarbonate. The organic layer was dried over sodium sulfate, filtered through silica gel and concentrated *in vacuo*. Recrystallization from diethyl ether afforded 45.6 mg (19%) of 3-(2-pyridyl)-5-(2-aminophenyl)-1,2,4-oxadiazole.

3-(2-pyridyl)-5-(2-aminophenyl)-1,2,4-oxadiazole

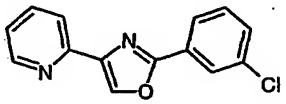
B49



In a similar fashion, 5-chloroisatoic anhydride (197 mg, 1 mmol) and pyrid-2-ylamidoxime (137 mg, 1 mmol) in pyridine (1 mL) was heated at 115 °C for 17 hours. Work up afforded 138 mg (51%) of 3-(2-pyridyl)-5-(2-aminophenyl)-1,2,4-oxadiazole.

2-[3-chlorophenyl]-4-[pyridin-2-yl]-1,3-oxazole

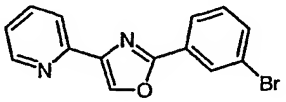
B50



Using the procedures of Kelly et al., *J. Org. Chem.*, (1996) *61*:4623-4633, a solution of 2-bromoacetylpyridine (120 mg, 0.6 mmol) in toluene (5mL) was treated with 3-chlorobenzamide (300 mg, 1.9 mmol) and the mixture heated in a sealed vial at reflux for 60 hours. The mixture was then cooled and the solvent was removed *in vacuo*. Silica gel chromatography using a gradient of hexane to ethyl acetate afforded 38 mg (9%) of 2-[3-chlorophenyl]-4-[pyridin-2-yl]-1,3-oxazole as a pale yellow solid. ^{1}H-NMR ($CDCl_3$), δ (ppm): 8.62 (d, 1H), 8.35 (s, 1H), 8.15 (m, 1H), 8.00 (m, 2H), 7.80 (td, 1H), 7.42 (m, 2H), 7.23 (m, 1H).

2-[3-Bromophenyl]-4-[pyridin-2-yl]-1,3-oxazole

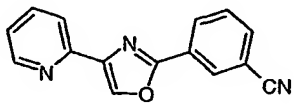
B51



In a similar fashion 2-bromoacetylpyridine (500 mg, 2.5 mmol) and 3-chlorobenzamide (1.2g, 6 mmol) in toluene (10 mL) was heated in a sealed vial at reflux for 60 hours. Work up and silica gel chromatography using a gradient of hexane to ethyl acetate afforded 50 mg (7%) of 2-[3-bromophenyl]-4-[pyridin-2-yl]-1,3-oxazole as a white solid. ^{1}H-NMR ($CDCl_3$), δ (ppm): 8.60 (d, 1H), 8.34 (s, 1H), 8.30 (t, 1H), 8.00 (m, 2H), 7.80 (td, 1H), 7.60 (dd, 1H), 7.35 (t, 1H), 7.23 (m, 1H).

2-[3-cyanophenyl]-4-[pyridin-2-yl]-1,3-oxazole

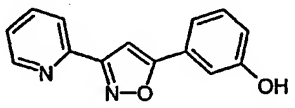
B52



A mixture of 2-[3-bromophenyl]-4-[pyridin-2-yl]-1,3-oxazole (23 mg, 0.076 mmol) and zinc cyanide (112 mg, 0.96 mmol) in *N,N*-dimethylformamide (2 mL) was treated with $Pd(PPh_3)_4$ (74 mg, 0.064 mmol) and heated overnight at 80°C. Standard work up and chromatography afforded 6 mg (32 %) of 2-[3-cyanophenyl]-4-[pyridin-2-yl]-1,3-oxazole as a white solid. ^{1}H-NMR ($CDCl_3$), δ (ppm): 8.61 (d, 1H), 8.45 (s, 1H), 8.38 (s, 1H), 8.36 (m, 1H),8.00 (d, 1H), 7.80 (m, 2H), 7.61 (t, 1H), 7.23 (m, 1H).

5-[3-hydroxyphenyl]-3-[pyridin-2-yl]-1,2-oxazole

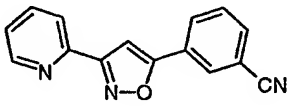
B53



A stirred solution of pyridine-2-carbohydroximoyl chloride (300 mg, 1.9 mmol) and 3-hydroxyphenylacetylene (760 mg, 6.4 mmol) in a 1:1 mixture of THF/CH_2Cl_2 (10 mL) at 0 °C was treated with triethylamine (2 mL, 1.45 g, 15 mmol). The mixture was allowed to warm to room temperature overnight. The solvent was removed *in vacuo*. The residue was dissolved in dichloromethane, washed with brine and dried over anhydrous sodium sulphate. Removal of the solvent *in vacuo* followed by trituation with 10% ethylacetate in hexane afforded 200 mg (44%) of 5-[3-hydroxyphenyl]-3-[pyridin-2-yl]-1,2-oxazole as a beige solid.

5-[3-cyanophenyl]-3-[pyridin-2-yl]-1,2-oxazole

B54

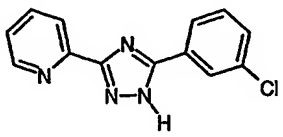


A mixture of 5-[3-trifluoromethanesulfonylphenyl]-3-[pyridin-2-yl]-1,2-oxazole (98 mg, 0.26 mmol), KCN (230 mg, 4 mmol), $NiBr_2(PPh_3)_2$ (52.4 mg, 0.07 mmol), and PPh_3 (42 mg, 0.16 mmol) in acetonitrile (1 mL) was treated with zinc powder (20 mg, 0.3 mmol) and the mixture was heated overnight at 60 °C. Silica gel chromatography of the resulting mixture using a gradient of hexane to ethyl acetate

afforded 15 mg (23 %) of 5-[3-cyanophenyl]-3-[pyridin-2-yl]-1,2-oxazole as a white solid.

3-(2-Pyridyl)-5-(3-chlorophenyl)-1,2,4-triazole

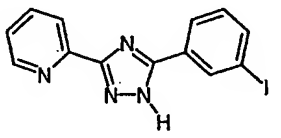
B55



Using the procedures of Browne et al., *Aust. J. Chem.*, (1975) *28*:2543-2546, a solution of 2-cyanopyridine (0.1 mL, 1.00 mmol) in methanol (5 mL) was treated with sodium metal (6.9 mg, 0.30 mmol) and stirred for at ambient temperature for 1 hour. After this time, a solution of 3-chlorobenzhyrazide (0.17 g, 1.0 mmol) in methanol (5 mL) was added and the resulting solution heated at reflux for 3 hours. The reaction mixture was concentrated *in vacuo*, and the resulting yellow solid (100 mg) dissolved in toluene (2 mL). The mixture was heated at 175 °C for 3 hours and then stirred overnight at ambient temperature. Evaporation of the solvent *in vacuo* and silica gel chromatography using 1% methanol in dichloromethane afforded 29 mg (11%) of 3-(2-pyridyl)-5-(3-chlorophenyl)-1,2,4-triazole as an off-white solid.

3-(2-Pyridyl)-5-(3-iodophenyl)-1,2,4-triazole

B56

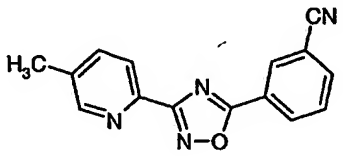


In a similar fashion, 2-cyanopyridine (0.15 mL, 1.53 mmol), sodium metal (10.5 mg, 0.46 mmol) and 3-iodobenzhydrazide (0.40 g, 1.53 mmol) afforded, after work up and chromatography, 210 mg (40%) of 3-(2-pyridyl)-5-(3-iodophenyl)-1,2,4-triazole as a white solid.

EXAMPLE 5

3-(5-Methyl-pyrid-2-yl)-5-(3-cyanophenyl)-1,2,4-oxadiazole

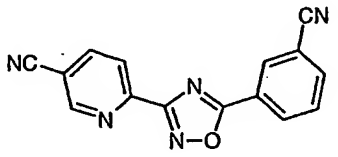
B57



A suspension of 5-methylpyrid-2-ylamidoxime (449.5 mg, 2.97 mmol) in dichloromethane (10 mL) was treated with 3-cyanobenzoyl chloride (495 mg, 2.99 mmol) and the mixture stirred 30 minutes. The solvent was removed *in vacuo* and the intermediate dissolved in *N,N*-dimethylformamide (15 mL). The reaction was heated, under an argon atmosphere, for 20 hours at 120 °C. After this time, the reaction mixture was cooled and the solvent removed *in vacuo*. Silica gel chromatography using a gradient of 20% to 75% ethyl acetate in hexane afforded 674 mg (86%) of 3-(5-methyl-pyrid-2-yl)-5-(3-cyanophenyl)-1,2,4-oxadiazole: ^{1}H-NMR ($CDCl_3$), δ (ppm): 8.69 (s, 1H), 8.60 (s, 1H), 8.51 (d, 1H), 8.12 (d, 1H), 7.90 (d, 1H), 7.72 (t, 2H).

3-(5-Cyano-pyrid-2-yl)-5-(3-cyanophenyl)-1,2,4-oxadiazole

B58



Method A: In a similar fashion, a solution of 5-tert-butoxycarbonylpyrid-2-ylamidoxime (89.5 mg, 0.38 mmol) in dichloromethane (5 mL) was treated with 3-cyanobenzoyl chloride (64.9 mg, 0.39 mmol) and stirred 2 minutes at room temperature. Saturated sodium bicarbonate (1 mL) was added and the resulting mixture stirred vigorously for 30 minutes. The mixture was passed through an EX-TUBE (3 mL) and the product was eluted with dichloromethane (25 mL). The organic wash was concentrated *in vacuo*, and the intermediate dissolved in *N,N*-dimethylformamide (2.5 mL). The solution was heated in sealed tube for 21 hours at 120 °C. After this time, the reaction mixture was added to ice cold water and

the crude oxadiazole collected and dried. Silica gel chromatography using a gradient of 10% to 30% ethyl acetate in hexane afforded 114.2 mg (87%) of 3-(5-tert-butoxycarbonyl-2-pyridyl)-5-(3-cyanophenyl)-1,2,4-oxadiazole.

Method B: A mixture of 3-(5-cyanopyridyl)amidoxime (95mg, 0.586 mmol) 3-cyanobenzoyl chloride (96mg, 0.586 mol) and triethylamine (175 mg, 1.74 mmol) in dichloromethane were stirred for 5 min. Then DMF (1ml) was added to the reaction mixture. The mixture was heated to 120 °C for 16 hrs. After cooling the mixture was poured into water. The solid was filtered and washed with water, then triturated in ether to provide 125 mg, (78%) of 3-(5-tert-butoxycarbonyl-2-pyridyl)-5-(3-cyanophenyl)-1,2,4-oxadiazole.

A mixture of 3-(5-*tert*-butoxycarbonylpyrid-2-yl)-5-(3-cyanophenyl)-1,2,4-oxadiazole (114 mg, 0.33 mmol) in formic acid (98%, 6 mL) was heated for 2 days at 45 °C. The incomplete reaction was resubjected to additional formic acid (96%, 6 mL) for 1 day at 45 °C. Co-evaporation of the solvent *in vacuo* using toluene afforded 103.6 mg of 3-(5-hydroxycarbonylpyrid-2-yl)-5-(3-cyanophenyl)-1,2,4-oxadiazole, as a white solid.

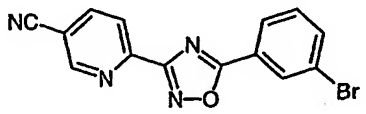
A suspension of 3-(5-hydroxycarbonylpyrid-2-yl)-5-(3-cyanophenyl)-1,2,4-oxadiazole (49.7 mg, 0.17 mmol) in dichloromethane (5 mL) was treated with 2M oxalyl chloride (0.19 mL, 0.38 mmol, dichloromethane) and a catalytic amount of *N,N*-dimethylformamide. The reaction was stirred at ambient temperature for 1 hour and solvents removed *in vacuo*. The acid chloride was dissolved in dichloromethane (5 mL) and treated with concentrated ammonium hydroxide (1 mL) for 1 hour. The aqueous layer was removed and the remaining organic solvent evaporating *in vacuo*, azeotroping with ethanol.

The crude amide in thionyl chloride (1.5 mL) was heated for 4.5 hours at 80 °C. After cooling, the excess thionyl chloride was removed *in vacuo* and the residue dissolved in dichloromethane. The organic solution was washed with aqueous sodium carbonate and dried by passing through an EX-TUBE. Silica gel chromatography using a gradient of 20% ethyl acetate in hexane to 100% ethyl acetate afforded 22.2 mg (47%) of 3-(5-cyano-pyrid-2-yl)-5-(3-cyanophenyl)-1,2,4-

oxadiazole: ^{1}H-NMR ($CDCl_3$), δ (ppm): 9.11 (s, 1H), 8.59 (s, 1H), 8.51 (d, 1H), 8.37 (d, 1H), 8.20 (dd, 1H), 7.94 (d, 1H), 7.75 (t, 1H).

3-(5-Cyano-2-pyridyl)-5-(3-bromophenyl)-1,2,4-oxadiazole

B59



A mixture of 3-bromobenzoyl chloride (0.17 mL, 1.28 mmol) and 5-tert-butoxycarbonylpyrid-2-ylamidoxime (302 mg, 1.27 mmol) in dichloromethane (10 mL) wasstirred at room temperature for 30 minutes. The solvent was removed *in vacuo*. The intermediate was dissolved in *N,N*-dimethylformamide (7.5 mL) and heated in sealed tube at 120 °C for 23 hours. The solvent was then removed *in vacuo*. Silica gel chromatography using a gradient of 5% to 10% ethyl acetate in hexane afforded 329 mg (64%) of 3-(5-tert-butoxycarbonyl-2-pyridyl)-5-(3-bromophenyl)-1,2,4-oxadiazole.

A mixture of 3-(5-*tert*-butoxycarbonylpyrid-2-yl)-5-(3-bromophenyl)-1,2,4-oxadiazole (100 mg, 0.25 mmol) in formic acid (98%, 6 mL) was heated at 45 °C for 23 hours. Evaporation of the solvent *in vacuo* followed by trituration with dichloromethane afforded 3-(5-hydroxycarbonylpyrid-2-yl)-5-(3-bromophenyl)-1,2,4-oxadiazole (65.4 mg, 76%) as a white solid.

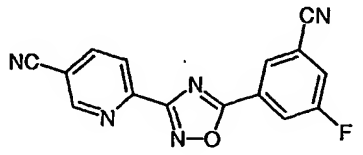
A mixture of 3-(5-hydroxycarbonylpyrid-2-yl)-5-(3-bromophenyl)-1,2,4-oxadiazole (269.4 mg, 0.78 mmol) in dichloromethane (15 mL) was treated with 2M oxalyl chloride (0.90 mL, 1.8 mmol, dichloromethane) and a catalytic amount *N,N*-dimethylformaide. The resulting mixture was stirred at ambient temperature for 1.5 hours and the solvent and excess oxalyl chloride removed, *in vacuo*. The acid chloride in dichloromethane (5 mL) was then treated with solid ammonium chloride (450 mg, 8.4 mmol) and pyridine (1.5 mL, 18.5 mmol). The mixture was stirred vigorously at ambient temperature for 15 hours, and then treated with 2M ammonia (5 mL, 10 mmol, methanol). The solvent was then removed *in vacuo*,

and the residue treated with water. Collection of the precipitate by filtration afforded crude 3-(5-aminocarbonylpyrid-2-yl)-5-(3-bromophenyl)-1,2,4-oxadiazole.

A solution of this intermediate amide in thionyl chloride (5 mL) was heated for 6 hours at 80 °C. After cooling, the excess thionyl chloride was removed *in vacuo*. The residue was dissolved in dichloromethane, washed with aqueous sodium carbonate and dried by passing through an EX-TUBE. Silica gel chromatography using a gradient of 5% to 30% ethyl acetate in hexane, afforded 130.8 mg (51%) of 3-(5-cyano-2-pyridyl)-5-(3-bromophenyl)-1,2,4-oxadiazole: ^{1}H-NMR ($CDCl_3$), δ (ppm): 9.10 (s, 1H), 8.45 (s, 1H), 8.36 (d, 1H), 8.18 (m, 2H), 7.78 (dd, 1H), 7.47 (t, 1H).

3-(5-Cyano-2-pyridyl)-5-(3-cyano-5-fluorophenyl)-1,2,4-oxadiazole

B60



Using the general procedure for the preparation of acid chlorides, 3-cyano-5-fluorobenzoyl chloride was prepared from 3-cyano-5-fluorobenzoic acid (106 mg, 0.63 mmol). The acid chloride in dichloromethane (2.5 mL) was treated with 5-tert-butoxycarbonylpyrid-2-ylamidoxime (149 mg, 0.63 mmol). The mixture stirred at room temperature for 2 hours and the solvent removed *in vacuo*. The intermediate was dissolved in *N,N*-dimethylformamide (2.5 mL) and heated in sealed tube for 13 hours at 120 °C. After cooling, water was added and the product collected by filtration. Silica gel chromatography using a gradient of 10% to 30% ethyl acetate in hexane afforded 71.2 mg (31%) of 3-(5-tert-butoxycarbonyl-2-pyridyl)-5-(3-cyano-5-fluorophenyl)-1,2,4-oxadiazole.

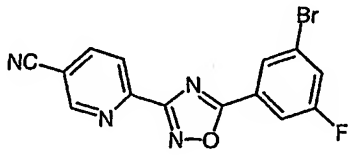
A mixture of 3-(5-*tert*-butoxycarbonylpyrid-2-yl)-5-(3-cyano-5-fluorophenyl)-1,2,4-oxadiazole (69 mg, 0.19 mmol) in formic acid (98%, 3.5 mL) was heated at 40 °C for 17 hours. Evaporation of the solvent *in vacuo* afforded crude 3-(5-

hydroxycarbonylpyrid-2-yl)-5-(3-cyano-5-flourophenyl)-1,2,4-oxadiazole as a white solid.

A solution of crude 3-(5-hydroxycarbonylpyrid-2-yl)-5-(3-cyano-5-flouorphenyl)-1,2,4-oxadiazole in dichloromethane (5 mL) was treated with 2M oxalyl chloride (0.25 mL, 0.5 mmol, dichloromethane) and a catalytic amount of N,N-dimethylformamide. The mixture was stirred at room temperature for 1.5 hour and the solvent and excess reagent removed *in vacuo*. The crude product was dissolved in dichloromethane (5 mL) and treated with 0.5M ammonia (2 mL, 1 mmol, dioxane). The mixture was stirred at room temperature for 1 hour and the solvents removed *in vacuo*. The crude amide, in dichloromethane (2 mL) and pyridine (0.10 mL, 1.23 mmol), was treated with trifluoroacetic anhydride (0.09 mL, 0.64 mmol). The mixture was stirred at room temperature for 12 hours and diluted with dichloromethane. The organic solution was washed with dilute aqueous sodium bicarbonate and brine, and dried over sodium sulfate and silica gel. Filtration and removal of the solvent *in vacuo* afforded the crude product. Silica gel chromatography using a gradient of 20% to 50% ethyl acetate in hexane, afforded 48.8 mg (88%) of 3-(5-cyano-2-pyridyl)-5-(3-cyano-5-fluorophenyl)-1,2,4-oxadiazole: ^{1}H-NMR ($CDCl_3$), δ (ppm):9.10 (s, 1H), 8.37 (m, 2H), 8.22 (m, 2H), 7.64 (m, 1H).

3-(5-Cyano-2-pyridyl)-5-(3-bromo-5-fluorophenyl)-1,2,4-oxadiazol

B61



Using the general procedure for the preparation of acid chlorides, 3-bromo-5-fluorobenzoyl chloride was prepared from 3-bromo-5-fluorobenzoic acid chloride (554 mg, 2.52 mmol). The acid chloride in dichloromethane (10 mL) was treated with 5-tert-butoxycarbonylpyrid-2-ylamidoxime (601 mg, 2.53 mmol). The mixture was stirred at room temperature for 30 minutes and the solvent was removed *in vacuo*. The intermediate was dissolved in DMF (15 mL) and heated in

sealed tube at 120 °C for 13 hours. After cooling the solvent was removed *in vacuo*. Silica gel chromatography using a gradient of 5% to 10% ethyl acetate in hexane, afforded 556 mg of crude 3-(5-tert-butoxycarbonyl-2-pyridyl)-5-(3-bromo-5-fluorophenyl)-1,2,4-oxadiazole.

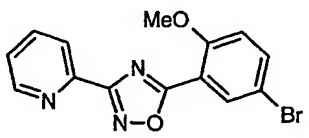
A mixture of this crude intermediate in formic acid (98%, 20 mL) was heated at 40 °C for 17 hours. Evaporation of the solvent *in vacuo* afforded 3-(5-hydroxycarbonylpyrid-2-yl)-5-(3-bromo-5-fluorophenyl)-1,2,4-oxadiazole as a white solid.

The crude acid in dichloromethane (20 mL) was treated with 2M oxalyl chloride (1.4 mL, 2.8 mmol, dichloromethane) and a catalytic amount of *N,N*-dimethylformamide. The mixture was stirred at room temperature for 2 hours and the solvent and excess reagent removed *in vacuo*. The crude product was dissolved in dichloromethane (25 mL) and and treated with 0.5M ammonia (10 mL, 5 mmol, dioxane) and the mixture stirred at room temperature for 1 hour. Removal of the solvent *in vacuo* afforded the crude amide.

The crude amide in a mixture of dichloromethane (7.5 mL) and pyridine (0.46 mL, 5.6 mmol) was treated with trifluoroacetic anhydride (0.44 mL, 3.1 mmol). The mixture was stirred at room temperature for 12 hours and then diluted with ethyl acetate. The organic solution was washed with dilute aqueous sodium bicarbonate and brine, and then dried over sodium sulfate and silica gel. Filtration and removal of the solvent *in vacuo* afforded the crude product. Silica gel chromatography using 10% ethyl acetate in hexane afforded 22 mg (6%) of 3-(5-cyano-2-pyridyl)-5-(3-bromo-5-fluorophenyl)-1,2,4-oxadiazole: ^{1}H-NMR ($CDCl_3$), δ (ppm): 9.10 (s, 1H), 8.36 (d, 1H), 8.25 (s, 1H), 8.18 (dd, 1H), 7.91 (dd, 1H), 7.53 (dd, 1H).

3-(2-Pyridyl)-5-(5-bromo-2-methoxyphenyl)-1,2,4-oxadiazole

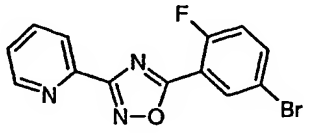
B62



A mixture of 5-bromo-2-methoxybenzoic acid (1.49 g, 6.45 mmol) in dichloromethane (10 mL) was treated with 2M oxalyl chloride (9.7 ml, 19.4 mmol, dichloromethane) and 3 drops of *N,N*-dimethylformamide. The mixture was stirred 4 hours at room temperature. The solvent and excess reagent were removed *in vacuo*. The residue was treated with pyrid-2-ylamidoxime (884 mg, 6.45 mmol) and triethylamine (1.95 g, 19.35 mmol) in dichloromethane (10 mL). The mixture was then heated in dimethylformamide (10 mL) for 2 hours at 120 °C. Standard work up, afforded 1.2 g (67%) of 3-(2-pyridyl)-5-(5-bromo-2-methoxyphenyl)-1,2,4-oxadiazole.

3-(2-Pyridyl)-5-(5-bromo-2-fluorophenyl)-1,2,4-oxadiazole

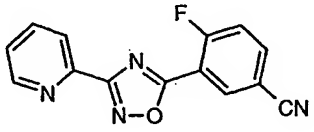
B63



In a similar fashion, 5-bromo-2-fluorobenzoyl chloride was prepared from 5-bromo-2-fluorobenzoic acid (2.19 g, 10 mmol). Treatment of the acid chloride with pyrid-2-ylamidoxime (1.37 g, 10 mmol) and triethylamine (3.03 g, 30 mmol) in dichloromethane (20 mL), followed by heating in dimethylformamide (20 mL) at 120 °C for 2 hours, afforded 3.2 g (100%) of 3-(2-pyridyl)-5-(5-bromo-2-fluorophenyl)-1,2,4-oxadiazole.

3-(2-Pyridyl)-5-(5-cyano-2-fluorophenyl)-1,2,4-oxadiazole

B64

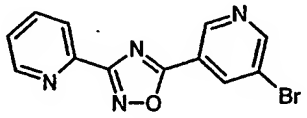


In a similar fashion, 5-cyano-2-fluorobenzoyl chloride was prepared from 5-cyano-2-fluorobenzoic acid (185 mg, 1.12 mmol). Treatment of the acid chloride with pyrid-2-ylamidoxime (1.153 g, 1.12 mmol) and triethylamine (340 mg, 3.36 mmol) in dichloromethane (3 mL), followed by heating in dimethylformamide (2 mL)

at 120 °C for 16 hours, afforded 17 mg (6%) of 3-(2-pyridyl)-5-(5-cyano-2-fluorophenyl)-1,2,4-oxadiazole.

3-(2-Pyridyl)-5-(5-bromopyrid-3-yl)-1,2,4-oxadiazole

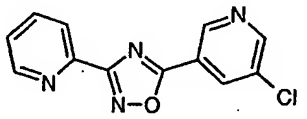
B65



In a similar fashion, 5-bromonicotinoyl chloride was prepared from 5-bromonicotinic acid (2.02 g, 10 mmol). Treatment of the acid chloride with pyrid-2-ylamidoxime (1.37 g, 10 mmol) and triethylamine (4.04 g, 40 mmol) in dichloromethane (20 mL), followed by heating in dimethylformamide (20 mL) at 120 °C for 16 hours. After this time water was added and the precipitate collected and dried. Filtration through silica gel using dichloromethane followed by trituration with hexane afforded 2.58 g (85%) of 3-(2-pyridyl)-5-(5-bromopyrid-3-yl)-1,2,4-oxadiazole.

3-(2-Pyridyl)-5-(5-chloro-pyrid-3-yl)-1,2,4-oxadiazole

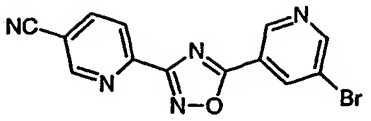
B66



In a similar fashion, 5-chloronicotinoyl chloride was prepared from 5-chloronicotinic acid (157 mg, 1 mmol). Treatment of the acid chloride with pyrid-2-ylamidoxime (137 mg, 1 mmol) and triethylamine (404 mg, 4 mmol) in dichloromethane (2 mL), followed by heating in dimethylformamide (2 mL) at 120 °C for 3 hours afforded 149 mg (58%) of 3-(2-pyridyl)-5-(5-chloro-pyrid-3-yl)-1,2,4-oxadiazole (149 mg, 57.6 %).

3-(5-Cyanopyrid-2-yl)-5-(5-bromo-pyrid-3-yl)-1,2,4-oxadiazole

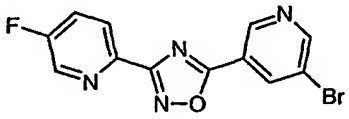
B67



In a similar fashion, 5-bromonicotinoyl chloride was prepared from 5-bromonicotinic acid (262.6 mg, 1.3 mmoles). Treatment of the acid chloride with 5-cyanopyrid-2-ylamidoxime (162 mg, 1 mmol) and triethylamine (404 mg, 4 mmol) in dichloromethane (2 mL), followed by heating in dimethylformamide (2 mL) at 120 °C for 16 hours afforded 230 mg (70%) of 3-(5-cyanopyrid-2-yl)-5-(5-bromo-pyrid-3-yl)-1,2,4-oxadiazole.

3-(5-Fluoropyrid-2-yl)-5-(5-bromo-pyrid-3-yl)-1,2,4-oxadiazole

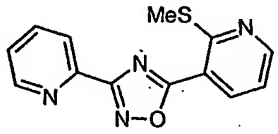
B68



In a similar fashion, 5-bromonicotinoyl chloride was prepared from 5-bromonicotinic acid (202 mg, 1 mmol). Treatment of the acid chloride with 5-fluoropyrid-2-ylamidoxime (155.13 mg, 1 mmol) and triethylamine (404 mg, 4 mmol) in dichloromethane (2 mL), followed by heating in dimethylformamide (2 mL) at 120 °C for 3 hours afforded 216.5 mg (67%) of 3-(5-fluoropyrid-2-yl)-5-(5-bromo-pyrid-3-yl)-1,2,4-oxadiazole.

3-(2-Pyridyl)-5-(2-thiomethoxy-pyrid-3-yl)-1,2,4-oxadiazole

B69

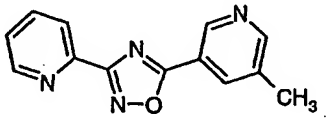


In a similar fashion, 2-thiomethoxynicotinoyl chloride was prepared from 2-thiomethoxynicotinic acid (169 mg, 1 mmol). Treatment of the acid chloride with pyrid-2-ylamidoxime (137mg, 1 mmole) and triethylamine (404 mg, 4 mmol) in dichloromethane (2 mL), followed by heating in dimethylformamide (2 mL) at 120

°C for 16 hours afforded 20 mg (7%) of 3-(2-pyridyl)-5-(2-thiomethoxy-pyrid-3-yl)-1,2,4-oxadiazole.

3-(2-Pyridyl)-5-(5-methylpyrid-3-yl)-1,2,4-oxadiazole

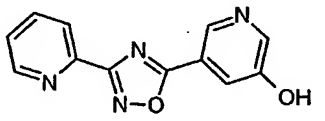
B70



In a similar fashion, 5-methylnicotinoyl chloride was prepared from 5-methylnicotinic acid (548 mg, 4 mmoles). Treatment of the acid chloride with pyrid-2-ylamidoxime (822 mg, 6 mmol) and triethylamine (1.2g, 12 mmol) in dichloromethane (6 mL), followed by heating in dimethylformamide (6 mL) at 120 °C for 2.5 hours, afforded 448 mg (47%) of 3-(2-pyridyl)-5-(5-methyl-pyrid-3-yl)-1,2,4-oxadiazole.

3-(2-Pyridyl)-5-(5-hydroxypyrid-3-yl)-1,2,4-oxadiazole

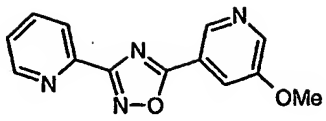
B71



In a similar fashion, 5-hydroxynicotinoyl chloride was prepared from 5-hydroxynicotinic acid hydrochloride, which was obtained form the hydrolysis of 5-hydroxynicotinic acid methyl ester (1.53 g, 10 mmol). Treatment of the acid chloride with pyrid-2-ylamidoxime (1.37 g, 10 mmol) and triethylamine (4.04g, 40 mmol) in dichloromethane (10 mL), followed by heating in dimethylformamide (20 mL) at 120 °C for 2 hours afforded 497 mg (21%) 3-(2-pyridyl)-5-(5-hydroxy-pyrid-3-yl)-1,2,4-oxadiazole.

3-(2-Pyridyl)-5-(5-methoxypyrid-3-yl)-1,2,4-oxadiazole

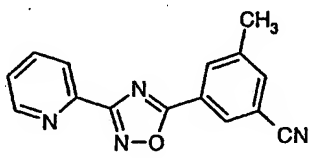
B72



In a similar fashion, 5-methoxynicotinoyl chloride was prepared from 5-methoxynicotinic acid hydrochloride (112.7 mg, 0.59 mmoles). Treatment of the acid chloride with pyrid-2-ylamidoxime (80.8 mg, 0.59 mmol) and triethylamine (0.3 mL) in dichloromethane (2 mL), followed by heating in dimethylformamide (1 mL) at 120 °C for 2.5 hours afforded 25 mg (17%) of 3-(2-pyridyl)-5-(5-methoxy-pyrid-3-yl)-1,2,4-oxadiazole.

3-(2-Pyridyl)-5-(3-cyano-5-methylphenyl)-1,2,4-oxadiazole

B73



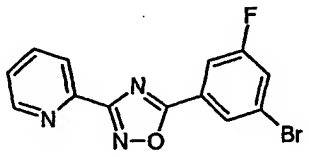
A solution of 5-methylisophalonitrile (1.0 g, 7.03 mmol) in methanol (9 mL) at 64 °C was treated dropwise with a solution of 20% NaOH (0.78 g, 19.5 mmol). The reaction was stirred an additional 14 hours at this temperature. Work up and silica gel chromatography, afforded 0.420 g (37%) of 3-cyano-5-methylbenzamide. The intermediate amide (0.110 g, 0.69 mmol) was treated with 70 wt.% H_2SO_4 (3.75 mL) and sodium nitrite (0.071 g, 1.03 mmol) and the mixture stirred at 40 °C for 1 hour. The reaction was cooled and the precipitate collected to afford 0.0447 g (42%) of 3-methyl-5-cyanobenzoic acid.

Using the general procedure for the preparation of acid chlorides, 3-methyl-5-cyanobenzoyl chloride was prepared from 3-methyl-5-cyanobenzoic acid (0.0447 g, 0.28 mmol). The acid chloride and pyrid-2-ylamidoxime (0.038 g, 0.28 mmol) in *N,N*-dimethylformamide (4 mL) was heated in sealed tube at 120 °C for 12 hours. Standard work up and silica gel chromatography afforded 0.480 g (80%) of 3-(2-pyridyl)-5-(3-cyano-5-methylphenyl)-1,2,4-oxadiazole: ^{1}H NMR ($CDCl_3$), δ (ppm):

8.85 (d, 1H), 8.36 (d, 2H), 8.22 (d, 1H), 7.89 (t, 1H), 7.70 (s, 1H), 7.48 (t, 1H), 2.52 (s, 3H),

3-(2-Pyridyl)-5-(3-fluoro-5-bromophenyl)-1,2,4-oxadiazole

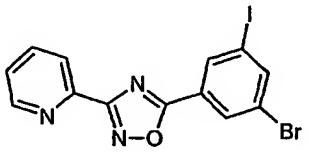
B74



Using the general procedure for the preparation of acid chlorides, 3-fluoro-5-bromobenzoyl chloride was prepared from 3-fluoro-5-bromobenzoic acid (300 mg, 1.369 mmol). The acid chloride was treated with pyrid-2-ylamidoxime (187.7 mg, 1.369 mmol) in pyridine (2 mL) and the mixture heated in sealed tube at 130 °C for 16 hours. After cooling, the reaction was treated with water and the solid collected by filtration. Recrystallization from ethanol afforded 168.3 mg (38%) of 3-(2-pyridyl)-5-(3-fluoro,5-bromophenyl)-1,2,4-oxadiazole: ^{1}H-NMR ($CDCl_3$), δ (ppm): 8.82 (d, 1H), 8.25 (s, 1H), 8.21 (d, 1H), 7.92 (td, 2H), 7.50 (m, 2H).

3-(2-Pyridyl)-5-(3-iodo-5-bromophenyl)-1,2,4-oxadiazole

B75

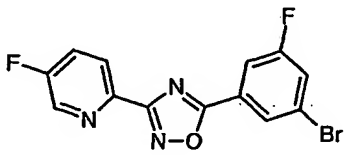


Using the general procedure for the preparation of acid chlorides, 3-iodo-5-bromobenzoyl chloride was prepared from 3-iodo-5-bromobenzoic acid (1.0 g, 3.058 mmol). The acid chloride was treated with pyrid-2-ylamidoxime (419.3 mg, 3.058 mmol) in pyridine (5 mL) and the mixture heated in sealed tube at 130 °C for 16 hours. After cooling, the reaction was treated with water and the solid collected by filtration. Recrystallization from ethanol afforded 140 mg (10.7%) of 3-(2-pyridyl)-5-(3-iodo-5-bromophenyl)-1,2,4-oxadiazole: ^{1}H-NMR ($CDCl_3$), δ (ppm):

8.84 (d, 1H), 8.57 (s, 1H), 8.42 (s, 1H), 8.22 (dd, 1H), 8.10 (s, 1H), 7.90 (t, 1H), 7.49 (td, 1H).

3-(5-Fluoro-2-pyridyl)-5-(3-fluoro-5-bromophenyl)-1,2,4-oxadiazole

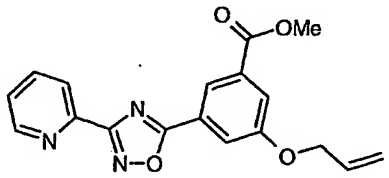
B76



Using the general procedure for the preparation of acid chlorides, 3-fluoro-5-bromobenzoyl chloride was prepared 3-fluoro-5-bromobenzoic acid (350 mg, 1.598 mmol). The acid chloride was treated 5-fluoropyrid-2-ylamidoxime (223 mg, 1.438 mmol) in dimethylformamide (5 mL) and the mixture heated in sealed tube at 130 °C for 16 hours. After cooling, the reaction was treated with water and the solid collected by filtration. Recrystallization from ethanol afforded 218 mg (45%) of 3-(5-fluoro-2-pyridyl)-5-(3-fluoro-5-bromophenyl)-1,2,4-oxadiazole: ^{1}H-NMR ($CDCl_3$), δ (ppm): 8.70 (d, 1H), 8.28 (s, 1H), 8.27 (dd, 1H), 7.93 (td, 1H), 7.61 (td, 1H), 7.53 (td, 1H).

3-(2-Pyridyl)-5-(3-allyloxy-5-(methoxycarbonyl)phenyl)-1,2,4-oxadiazole

B77

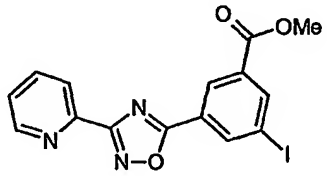


Using the general procedure for the preparation of acid chlorides, 3-allyloxy-5-(methoxycarbonyl)benzoyl chloride was prepared from 3-allyloxy-5-(methoxycarbonyl)benzoic acid (3.24 g, 13.7 mmol). A solution of the acid chloride in dichloromethane (20 mL) at 0°C was treated with pyrid-2-ylamidoxime (1.9 g, 13.9 mmol) and then stirred at ambient temperature for 2 hours. After this time, the reaction mixture was washed with water and saturated brine, dried over anhydrous sodium sulfate, filtered, and concentrated. The residue was dissolved in

N,N-dimethylformamide (50 mL) and heated at 120 °C for 16 hours. Standard work up and silica gel chromatography using hexanes:ethyl acetate:dichloromethane (3.5:0.5:4) afforded 1.8 g (39%) of 3-(2-pyridyl)-5-(3-allyloxy-5-(methoxycarbonyl)phenyl)-1,2,4-oxadiazole: ^{1}H NMR (DMSO): δ - 8.81 (d, 1H), 8.28 (s, 1H), 8.20 (d, 1H), 8.07 (t, 1H), 7.94 (s, 1H), 7.76 (s, 1H), 7.66 (m, 2H), 6.09 (m, 1H), 5.47 (dd, 1H), 5.33 (dd, 1H), 4.81 (d, 2H), 3.93 (s, 3H).

3-(2-Pyridyl)-5-(3-iodo-5-(methoxycarbonyl)phenyl)-1,2,4-oxadiazole

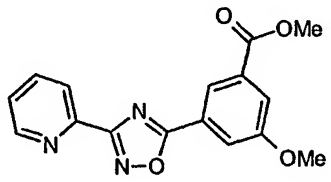
B78



Using the general procedure for the preparation of acid chlorides, 3-iodo-5-(methoxycarbonyl)benzoyl chloride was prepared from 3-iodo-5-(methoxycarbonyl)benzoic acid (1.7 g, 5.554 mmol). The acid chloride was treated with pyrid-2-ylamidoxime (0.685 g, 4.998 mmol) in dimethylformamide (10 mL) and the mixture heated in sealed tube at 130 °C for 16 hours. After cooling, the reaction was treated with water and the solid collected by filtration. Recrystallization from ethanol afforded 357 mg (17.8%) of 3-(2-pyridyl)-5-(3-iodo-5-(methoxycarbonyl)phenyl)-1,2,4-oxadiazole: ^{1}H-NMR ($CDCl_3$), δ (ppm): 8.85 (s, 1H), 8.84 (m, 1H), 8.82 (m, 1H), 8.60 (s, 1H), 8.25 (dd, 1H), 7.91 (td, 1H), 7.50 (dd, 1H), 4.05 (s, 3H).

3-(2-Pyridyl)-5-(3-methoxy-5-(methoxycarbonyl)phenyl)-1,2,4-oxadiazole

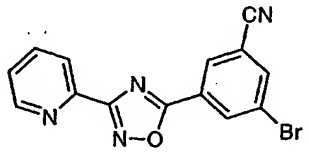
B79



Using the general procedure for the preparation of acid chlorides, 3-methoxy-5-(methoxycarbonyl)benzoyl chloride was prepared from 3-methoxy-5-(methoxycarbonyl)benzoic acid (400 mg, 1.9 mmol). The acid chloride in dichloromethane (20 mL) at 0 °C was treated with pyrid-2-ylamidoxime (261 mg, 1.9 mmol) and the mixture stirred at room temperature for 1 hour. The reaction mixture was then washed with water and saturated brine, dried over anhydrous sodium sulfate, filtered, and concentrated. The residue was dissolved in *N,N*-dimethylformamide (4 mL) and heated overnight at 110 °C. Standard work up and silica gel chromatography using a mixture of hexane:ethyl acetate:dichloromethane (3:1:4) afforded 191.3 mg (32%) of 3-(2-pyridyl)-5-(3-methoxy-5-(methoxycarbonyl)phenyl)-1,2,4-oxadiazole: ^{1}H NMR ($CDCl_3$): δ - 8.86 (d, 1H), 8.55 (s, 1H), 8.25 (d, 1H), 7.99 (m, 1H), 7.90 (t, 1H), 7.82 (s, 1H), 7.47 (m, 1H), 3.98 (s, 3H), 3.96 (s, 3H).

3-(2-Pyridyl)-5-(3-bromo-5-cyanophenyl)-1,2,4-oxadiazole

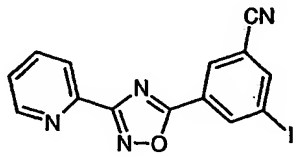
B80



Using the general procedure for the preparation of acid chlorides, 3-bromo-5-cyanobenzoyl chloride was prepared from 3-bromo-5-cyanobenzoic acid (1.6 g, 7.0 mmol). The acid chloride in dichloromethane (20 mL) at 0 °C was treated with pyrid-2-ylamidoxime (965 mg, 7.0 mmol) and the mixture stirred at room temperature for 2 hours. The reaction mixture was washed with water and saturated brine, dried over anhydrous sodium sulfate, filtered, and concentrated. The residue was dissolved in *N,N*-dimethylformamide (30 mL) and heated overnight at 110 °C. Standard work up and silica gel chromatography using a mixture of hexane:ethyl acetate:dichloromethane (3:1:4) afforded 739 g (32 %) of 3-(2-pyridyl)-5-(3-bromo-5-cyanophenyl)-1,2,4-oxadiazole: ^{1}H NMR ($CDCl_3$): δ - 8.87 (d, 1H), 8.70 (s, 1H), 8.52 (s, 1H), 8.23 (d, 1H), 8.03 (s, 1H), 7.92 (t, 1H), 7.51 (m, 1H).

3-(2-Pyridyl)-5-(5-cyano-3-iodophenyl)-1,2,4-oxadiazole

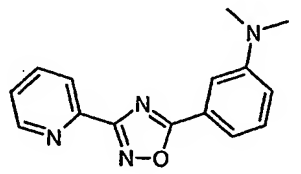
B81



Using the general procedure for the preparation of acid chlorides, 3-cyano-5-iodobenzoyl chloride was prepared from 3-cyano-5-iodobenzoic acid (570 mg, 2.1 mmol). The acid chloride in dichloromethane (5 mL) was treated with pyrid-2-ylamidoxime (287 mg, 2.1 mmol) and triethylamine (1 mL) and the mixture stirred for 1 hour at room temperature. The solvent was removed *in vacuo*, and the residue dissolved in *N,N*-dimethylformamide (5 mL). The mixture was heated overnight at 120 °C. Removal of the solvent *in vacuo*, and trituration with 20% ethylacetate in hexane afforded 250 mg (32% yield) of 3-(2-pyridyl)-5-(5-cyano-3-iodophenyl)-1,2,4-oxadiazole: ^{1}H-NMR ($CDCl_3$), δ ppm: 8.85 (m, 2H), 8.54 (s, 1H), 8.22 (d, 1H), 8.20 (s, 1H), 7.90 (t, 1H), 7.45 (m, 1H). GC/EI-MS gave m/z 374 (M^+)

3-(2-Pyridyl)-5-(3-*N,N*-dimethylaminophenyl)-1,2,4-oxadiazole

B82

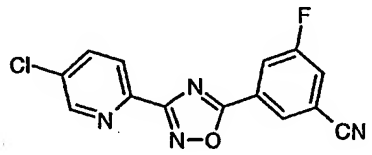


Using the general procedure for the preparation of acid chlorides, 3-dimethylaminobenzoyl chloride was prepared from 3-dimethylaminobenzoic acid (632 mg, 3.1 mmol). The acid chloride in dichloromethane (20 mL) at 0 °C was treated with pyrid-2-ylamidoxime (430 mg, 3.1 mmol). The mixture was then stirred at room temperature for 2 hours. Standard work up afforded a residue which was dissolved in *N,N*-dimethylformamide (15 mL) and heated overnight at 110 °C. After cooling, the solvent was removed *in vacuo*. The residue was

dissolved in dichloromethane and then washed with water and saturated brine, dried over anhydrous sodium sulfate, filtered and concentrated. Silica gel chromatography using a mixture of hexane:ethyl acetate:dichloromethane (3:1:4) followed by trituration with 10 % diethyl ether in hexane, afforded 27 mg (3 %) of 3-(2-pyridyl)-5-(3-N,N-dimethylaminophenyl)-1,2,4-oxadiazole: ^{1}H NMR ($CDCl_3$): δ - 8.86 (d, 1H), 8.24 (d, 1H), 7.88 (t, 1H), 7.60 (m, 2H), 7.46 (m, 1H), 7.37 (m, 1H), 6.95 (d, 1H), 3.06 (s, 6H).

3-(5-Chloropyrid-2-yl)-5-(3-cyano-5-fluorophenyl)-1,2,4-oxadiazole

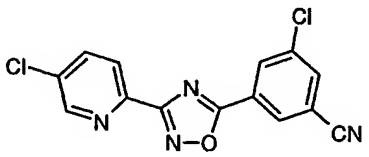
B83



Using the general procedure for the preparation of acid chlorides, 3-cyano-5-fluorobenzoyl chloride was prepared from 3-cyano-5-fluorobenzoic acid (0.10 g, 0.6 mMol). Treatment of the intermediate acid chloride in dichloromethane with 5-chloropyrid-2-ylamidoxime (0.103 g, 0.6 mMol) followed by heating in *N,N*-dimethylformamide overnight at 110 °C afforded crude product. Standard work up and purification by silica gel chromatography, and recrystallization afforded 30 mg (16%) 3-(5-chloropyrid-2-yl)-5-(3-cyano-5-fluorophenyl)-1,2,4-oxadiazole.

3-(5-Chloropyrid-2-yl)-5-(3-cyano-5-chlorophenyl)-1,2,4-oxadiazole

B84

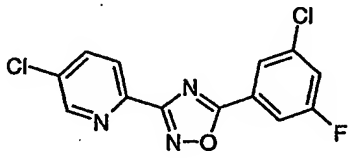


Using the general procedure for the preparation of acid chlorides, 3-cyano-5-chlorobenzoyl chloride was prepared from 3-cyano-5-chlorobenzoic acid (0.10 g, 0.55 mMol). Treatment of the intermediate acid chloride in dichloromethane with 5-

chloropyrid-2-ylamidoxime (0.094 g, 0.55 mMol) followed by heating in *N,N*-dimethylformamide overnight at 110 °C afforded crude product. Standard work up and purification by silica gel chromatography, and recrystallization afforded 4.5 mg (2.6%) 3-(5-chloropyrid-2-yl)-5-(3-cyano-5-chlorophenyl)-1,2,4-oxadiazole.

3-(5-Chloropyrid-2-yl)-5-(3-chloro-5-fluorophenyl)-1,2,4-oxadiazole

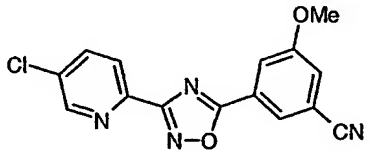
B85



Using the general procedure for the preparation of acid chlorides, 3-chloro-5-fluorobenzoyl chloride is prepared from 3-chloro-5-fluorobenzoic acid using a solution of oxalyl chloride in dichloromethane and a catalytic amount of *N,N*-dimethylformamide. Treatment of the intermediate acid chloride in dichloromethane with 1 equivalent of 5-chloropyrid-2-ylamidoxime followed by heating in *N,N*-dimethylformamide overnight at 110 °C affords crude product. Standard work up and purification by one or more methods, including silica gel chromatography, recystallization, and trituration, affords purified 3-(5-chloropyrid-2-yl)-5-(3-chloro-5-fluorophenyl)-1,2,4-oxadiazole.

3-(5-Chloropyrid-2-yl)-5-(3-cyano-5-methoxyphenyl)-1,2,4-oxadiazole

B86

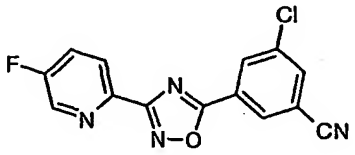


Using the general procedure for the preparation of acid chlorides, 3-cyano-5-methoxybenzoyl chloride is prepared from 3-cyano-5-methoxybenzoic acid using a solution of oxalyl chloride in dichloromethane and a catalytic amount of *N,N*-dimethylformamide. Treatment of the intermediate acid chloride in dichloromethane with 1 equivalent of 5-chloropyrid-2-ylamidoxime followed by

heating in *N,N*-dimethylformamide overnight at 110 °C affords crude product. Standard work up and purification by one or more methods, including silica gel chromatography, recystallization, and trituration, affords purified 3-(5-chloropyrid-2-yl)-5-(3-cyano-5-methoxyphenyl)-1,2,4-oxadiazole.

3-(5-Fluoropyrid-2-yl)-5-(3-cyano-5-chlorophenyl)-1,2,4-oxadiazole

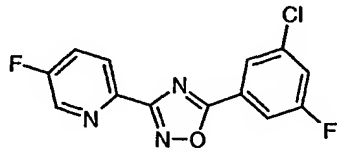
B87



Using the general procedure for the preparation of acid chlorides, 3-cyano-5-chlorobenzoyl chloride was prepared from 3-cyano-5-chlorobenzoic acid (0.10 g, 0.55 mMol). Treatment of the intermediate acid chloride in dichloromethane with 5-flouropyrid-2-ylamidoxime (0.086 g, 0.55 mMol) followed by heating in *N,N*-dimethylformamide overnight at 110 °C afforded crude product. Standard work up and purification by silica gel chromatography, and recrystallization afforded 1.8 mg (1%) 3-(5-fluoropyrid-2-yl)-5-(3-cyano-5-chlorophenyl)-1,2,4-oxadiazole.

3-(5-Fluoropyrid-2-yl)-5-(3-fluoro-5-chlorophenyl)-1,2,4-oxadiazole

B88

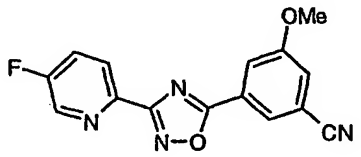


Using the general procedure for the preparation of acid chlorides, 3-chloro-5-fluorobenzoyl chloride is prepared from 3-chloro-5-fluorobenzoic acid using a solution of oxalyl chloride in dichloromethane and a catalytic amount of *N,N*-dimethylformamide. Treatment of the intermediate acid chloride in dichloromethane with 1 equivalent of 5-fluoropyrid-2-ylamidoxime followed by heating in *N,N*-dimethylformamide overnight at 110 °C affords crude product. Standard work up and purification by one or more methods, including silica gel

chromatography, recystallization, and trituration, affords purified 3-(5-fluororopyrid-2-yl)-5-(3-chloro-5-fluorophenyl)-1,2,4-oxadiazole.

3-(5-Fluoropyrid-2-yl)-5-(3-cyano-5-methoxyphenyl)-1,2,4-oxadiazole

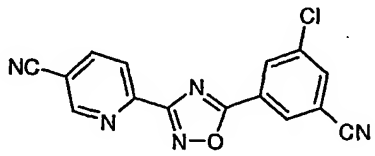
B89



Using the general procedure for the preparation of acid chlorides, 3-cyano-5-methoxybenzoyl chloride is prepared from 3-cyano-5-methoxybenzoic acid using a solution of oxalyl chloride in dichloromethane and a catalytic amount of *N,N*-dimethylformamide. Treatment of the intermediate acid chloride in dichloromethane with 1 equivalent of 5-fluoropyrid-2-ylamidoxime followed by heating in *N,N*-dimethylformamide overnight at 110 °C affords crude product. Standard work up and purification by one or more methods, including silica gel chromatography, recystallization, and trituration, affords purified 3-(5-fluororopyrid-2-yl)-5-(3-cyano-5-methoxyphenyl)-1,2,4-oxadiazole.

3-(5-Cyanopyrid-2-yl)-5-(3-cyano-5-chlorophenyl)-1,2,4-oxadiazole

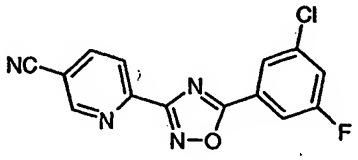
B90



Using the general procedure for the preparation of acid chlorides, 3-cyano-5-chlorobenzoyl chloride was prepared from 3-cyano-5-chlorobenzoic acid (0.10 g, 0.55 mMol). Treatment of the intermediate acid chloride in dichloromethane with 5-cyanopyrid-2-ylamidoxime (0.099 g, 0.55 mMol) followed by heating in *N,N*-dimethylformamide overnight at 110 °C afforded crude product. Standard work up and purification by silica gel chromatography, and recrystallization afforded 1.1 mg (0.65%) 3-(5-fluoropyrid-2-yl)-5-(3-cyano-5-chlorophenyl)-1,2,4-oxadiazole.

3-(5-Cyanopyrid-2-yl)-5-(3-fluoro-5-chlorophenyl)-1,2,4-oxadiazole

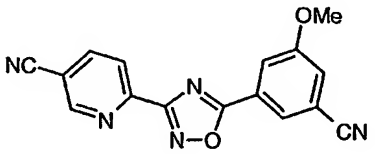
B91



Using the general procedure for the preparation of acid chlorides, 3-chloro-5-fluorobenzoyl chloride is prepared from 3-chloro-5-fluorobenzoic acid using a solution of oxalyl chloride in dichloromethane and a catalytic amount of *N,N*-dimethylformamide. Treatment of the intermediate acid chloride in dichloromethane with 1 equivalent of 5-cyanopyrid-2-ylamidoxime followed by heating in *N,N*-dimethylformamide overnight at 110 °C affords crude product. Standard work up and purification by one or more methods, including silica gel chromatography, recystallization, and trituration, affords purified 3-(5-cyanopyrid-2-yl)-5-(3-chloro-5-fluorophenyl)-1,2,4-oxadiazole.

3-(5-Cyanopyrid-2-yl)-5-(3-cyano-5-methoxyphenyl)-1,2,4-oxadiazole

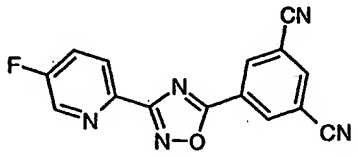
B92



cyano-5-methoxybenzoic acid using a solution of oxalyl chloride in dichloromethane and a catalytic amount of *N,N*-dimethylformamide. Treatment of the intermediate acid chloride in dichloromethane with 1 equivalent of 5-cyanopyrid-2-ylamidoxime followed by heating in *N,N*-dimethylformamide overnight at 110 °C affords crude product. Standard work up and purification by one or more methods, including silica gel chromatography, recystallization, and trituration, affords purified 3-(5-cyanopyrid-2-yl)-5-(3-cyano-5-methoxyphenyl)-1,2,4-oxadiazole.

3-(5-Fluoropyrid-2-yl)-5-(3,5-di-cyanophenyl)-1,2,4-oxadiazole

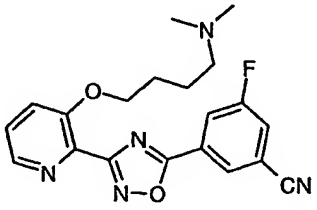
B93



Using the general procedure for the preparation of acid chlorides, 3,5-dicyanobenzoyl chloride is prepared from 3,5-dicyanobenzoic acid using a solution of oxalyl chloride in dichloromethane and a catalytic amount of *N,N*-dimethylformamide. Treatment of the intermediate acid chloride in dichloromethane with 1 equivalent of 5-fluoropyrid-2-ylamidoxime followed by heating in *N,N*-dimethylformamide overnight at 110 °C affords crude product. Standard work up and purification by one or more methods, including silica gel chromatography, recystallization, and trituration, affords purified 3-(5-fluoropyrid-2-yl)-5-(3,5-dicyanophenyl)-1,2,4-oxadiazole.

3-(3-(4-Dimethylaminobutoxy)-pyrid-2-yl)-5-(3-cyano-5-fluorophenyl)-1,2,4-oxadiazole

B94



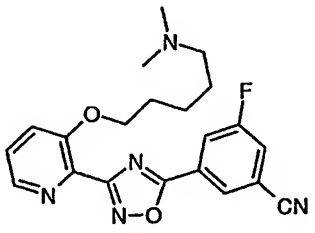
Using the general procedure for the preparation of acid chlorides, 3-cyano-5-fluorobenzoyl chloride is prepared from 3-cyano-5-fluorobenzic acid using a solution of oxalyl chloride in dichloromethane and a catalytic amount of *N,N*-dimethylformamide. Treatment of the intermediate acid chloride in dichloromethane with 1 equivalent of 3-(4-dimethylaminobutoxy)pyrid-2-ylamidoxime followed by heating in *N,N*-dimethylformamide overnight at 110 °C affords crude product. Standard work up and purification by one or more methods,

including silica gel chromatography, recystallization, trituration, and reversed-phase high-performance liquid chromatography (RP-HPLC) affords purified 3-(3-(4-dimethylaminobutoxy)-pyrid-2-yl)-5-(3-cyano-5-fluorophenyl)-1,2,4-oxadiazole.

Alternatively, treatment of 3-(3-fluoropyrid-2-yl)-5-(3-fluoro-5-cyanophenyl)-1,2,4-oxadiazole with potassium 4-dimethylaminobutoxide in *N.N*-dimethylformamide with a catalytic amount of 1,4,7,10,13,16-hexaoxacyclooctadecane (18-crown-6) and heating at 110 °C affords crude product. Standard work up and purification by one or more methods, including silica gel chromatography, recystallization, trituration, and reversed-phase high-performance liquid chromatography (RP-HPLC) affords purified 3-(3-(4-dimethylaminobutoxy)-pyrid-2-yl)-5-(3-cyano-5-fluorophenyl)-1,2,4-oxadiazole.

3-(3-(5-Dimethylaminopentyloxy)-pyrid-2-yl)-5-(3-Cyano-5-fluorophenyl)-1,2,4-oxadiazole

B95

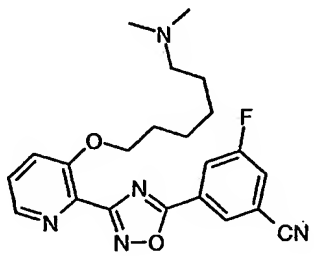


Using the general procedure for the preparation of acid chlorides, 3-cyano-5-fluorobenzoyl chloride is prepared from 3-cyano-5-fluorobenzic acid using a solution of oxalyl chloride in dichloromethane and a catalytic amount of *N,N*-dimethylformamide. Treatment of the intermediate acid chloride in dichloromethane with 1 equivalent of 3-(5-dimethylaminopentyloxy)pyrid-2-ylamidoxime followed by heating in *N,N*-dimethylformamide overnight at 110 °C affords crude product. Standard work up and purification by one or more methods, including silica gel chromatography, recystallization, trituration, and reversed-phase high-performance liquid chromatography (RP-HPLC) affords purified 3-(3-(5-dimethylaminopentyloxy)-pyrid-2-yl)-5-(3-cyano-5-fluorophenyl)-1,2,4-oxadiazole.

Alternatively, treatment of 3-(3-fluoropyrid-2-yl)-5-(3-fluoro-5-cyanophenyl)-1,2,4-oxadiazole with potassium 5-dimethylaminopentyloxide in *N,N*-dimethylformamide with a catalytic amount of 1, 4, 7, 10, 13, 16-hexaoxacyclooctadecane (18-crown-6) and heating at 110 °C affords crude product. Standard work up and purification by one or more methods, including silica gel chromatography, recystallization, trituration, and reversed-phase high-performance liquid chromatography (RP-HPLC) affords purified 3-(3-(5-dimethylaminopentyloxy)-pyrid-2-yl)-5-(3-cyano-5-fluorophenyl)-1,2,4-oxadiazole.

3-(3-(6-Dimethylaminohexyloxy)-pyrid-2-yl)-5-(3-cyano-5-fluorophenyl)-1,2,4-oxadiazole

B96



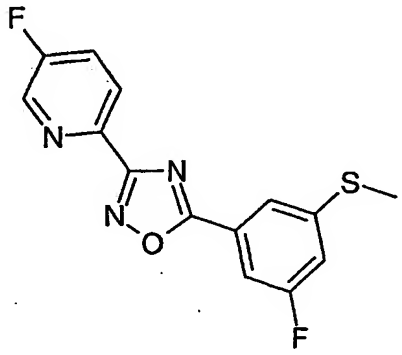
Using the general procedure for the preparation of acid chlorides, 3-cyano-5-fluorobenzoyl chloride is prepared from 3-cyano-5-fluorobenzic acid using a solution of oxalyl chloride in dichloromethane and a catalytic amount of *N,N*-dimethylformamide. Treatment of the intermediate acid chloride in dichloromethane with 1 equivalent of 3-(6-dimethylaminohexyloxy)pyrid-2-ylamidoxime followed by heating in *N,N*-dimethylformamide overnight at 110 °C affords crude product. Standard work up and purification by one or more methods, including silica gel chromatography, recystallization, trituration, and reversed-phase high-performance liquid chromatography (RP-HPLC) affords purified 3-(3-(6-dimethylaminohexyloxy)-pyrid-2-yl)-5-(3-cyano-5-fluorophenyl)-1,2,4-oxadiazole.

Alternatively, treatment of 3-(3-fluoropyrid-2-yl)-5-(3-fluoro-5-cyanophenyl)-1,2,4-oxadiazole with potassium 6-dimethylaminohexyloxide in *N,N*-dimethylformamide with a catalytic amount of 1,4,7,10,13,16-hexaoxacyclooctadecane (18-crown-6) and heating at 110 °C affords crude

product. Standard work up and purification by one or more methods, including silica gel chromatography, recystallization, trituration, and reversed-phase high-performance liquid chromatography (RP-HPLC) affords purified 3-(3-(6-dimethylaminohexyloxy)-pyrid-2-yl)-5-(3-cyano-5-fluorophenyl)-1,2,4-oxadiazole.

3-(5-Fluoropyrid-2-yl)-5-(5-fluoro-3-(thiomethyl)phenyl)-1,2,4-oxadiazole

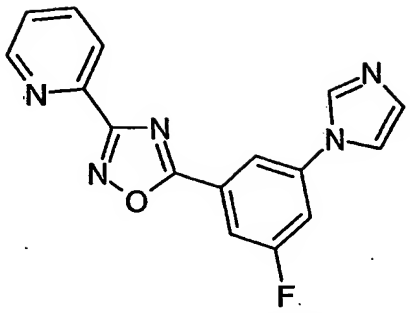
B153



Using the general procedure for the preparation of acid chlorides 5-fluoro-3-(thiomethyl)benzoyl chloride was prepared from 5-fluoro-3-(thiomethyl)benzoic acid using a solution of oxalyl chloride in dichloromethane and a catalytic amount of *N,N*-dimethylformamide. Treatment of the intermediate acid chloride in dichloromethane with 1 equivalent of 5-fluoropyrid-2-ylamidoxime followed by heating in *N,N*-dimethylformamide overnight at 110 °C afforded crude product. Standard work up and purification by silica gel chromatography afforded the purified title compound in 52 mg yield (64%) as a colourless solid.

5-(2-Pyridyl)-3-[3-(1*H*-imidazol-1-yl)-5-Fluorophenyl)]-1,2,4-oxadiazole

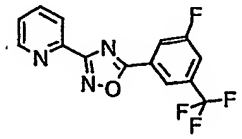
B154



Using the general procedure for the preparation of acid chlorides 3-fluoro-5-(1*H*-imidazol-1-yl)benzoyl chloride was prepared from 3-fluoro-5-(1*H*-imidazol-1-yl)benzoic acid using a solution of oxalyl chloride in dichloromethane and a catalytic amount of *N,N*-dimethylformamide. Treatment of the intermediate acid chloride in dichloromethane with 1 equivalent of 2-pyridylamidoxime followed by heating in *N,N*-dimethylformamide overnight at 110 °C afforded crude product. Standard work up and purification by silica gel chromatography followed by preperative reversed-phase HPLC afforded the title compound in 6.9 mg yield (5% over 4 steps) as a colourless solid.

3-(2-Pyridyl)-5-(3-cyano-5-trifluoromethylphenyl)-1,2,4-oxadiazole

B155

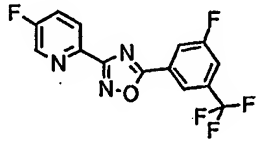


3-Fluoro-5-trifluoromethylbenzoyl chloride (0.11 mL, 0.73 mmol) was added in a dropwise manner to a solution of pyridylamidoxime (99.3 mg, 0.73 mmol) in dichloromethane (10 mL) under argon. The reaction mixture was stirred at room temperature for 10 minutes and the solvent was removed *in vacuo*. DMF (4 ml) was added to the oily residue and the resulting solution was stirred at 120°C for 16 h under argon. After the reaction mixture was cooled to room temperature, the solvent was removed *in vacuo*. Flash chromatography on silica gel (15%-20% ethyl acetate in hexanes) yielded 150 mg (66.9%, GC/MS product RT 7.59 min,

98% purity) of 3-(2-pyridyl)-5-(3-cyano-5-trifluoromethylphenyl)-1,2,4-oxadiazole. ^{1}H-NMR ($CDCl_3$), δ (ppm): 8.86 (d, 1H), 8.40 (s, 1H), 8.24 (d, 1H), 8.18 (d, 1H), 7.90 (dt, 1H), 7.59 (d, 1H), 7.49 (m, 1H).

3-(5-Fluoro-2-pyridyl)-5-(3-fluoro-5-trifluoromethylphenyl)-1,2,4-oxadiazole

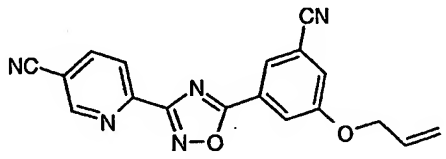
B156



3-Fluoro-5-trifluoromethylbenzoyl chloride (0.10 mL, 0.65 mmol) was added to a solution of 5-fluoropyridylamidoxime (102.9 mg, 0.66 mmol) in dichloromethane (2 mL). The solution was stirred at room temperature for 10 minutes and then concentrated *in vacuo*. DMF (4mL) was added to the residue and the resulting solution was stirred at 120°C for 16 h under argon. After the reaction mixture was cooled to room temperature, the solvent was removed *in vacuo*. Flash chromatography on silica gel (10%-20% ethyl acetate in hexane) yielded 131.1 mg (62.5%, GC/MSproduct RT 7.34 min, 96% pure) of 3-(5-fluoro-2-pyridyl)-5-(3-fluoro-5-trifluoromethylphenyl)-1,2,4-oxadiazole. ^{1}H-NMR ($CDCl_3$), δ (ppm): 8.70 (d, 1H), 8.38 (s, 1H), 8.28 (dd, 1H), 8.17 (d, 1H), 7.60 (dt, 2H).

3-(5-Cyanopyrid-2-yl)-5-(3-alloxy-5-cyanophenyl)-1,2,4-oxadiazole

B157

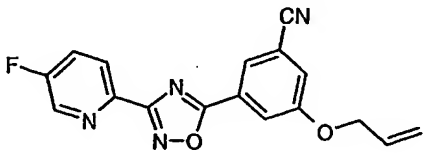


Using the general procedure for the preparation of acid chlorides, 3-allyloxy-5-cyanobenzoyl chloride was prepared from 3-allyloxy-5-cyanobenzoic acid (203 mg, 1.0 mmol). A solution of the acid chloride in dichloromethane (2 mL) at 0°C was treated with 5-cyanopyrid-2-ylamidoxime (162 mg, 1.0 mmol) and

triethylamine (418 µL, 3.0 mmol) and then stirred at ambient temperature for 1 hour. The reaction mixture was washed with water and saturated brine, dried over anhydrous sodium sulfate, filtered, and concentrated. The residue was dissolved in *N,N*-dimethylformamide (5 mL) and heated at 120 °C for 16 hours. Standard work up and silica gel chromatography using hexanes:ethyl acetate:dichloromethane (3.5:0.5:4) afforded 131 mg (40%) of 3-(5-cyanopyrid-2-yl)-5-(3-allyloxy-5-cyanophenyl)-1,2,4-oxadiazole: ^{1}H NMR ($CDCl_3$), δ (ppm): 9.11 (d, 1H), 8.39 (d, 1H), 8.22 (s, 1H), 8.21 (d, 1H), 8.01 (s, 1H), 7.42 (s, 1H), 6.05 (m, 1H), 4.48 (dd, 1H), 4.40 (dd, 1H), 4.69 (d, 2H).

3-(5-fluoropyrid-2-yl)-5-(3-alloxy-5-cyanophenyl)-1,2,4-oxadiazole

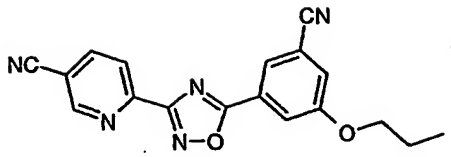
B158



Using the general procedure for the preparation of acid chlorides, 3-allyloxy-5-cyanobenzoyl chloride was prepared from 3-allyloxy-5-cyanobenzoic acid (203 mg, 1.0 mmol). A solution of the acid chloride in dichloromethane (2 mL) at 0°C was treated with 5-fluoropyrid-2-ylamidoxime (155 mg, 1.0 mmol) and triethylamine (418 µL, 3.0 mmol) and then stirred at ambient temperature for 1 hour. The reaction mixture was washed with water and saturated brine, dried over anhydrous sodium sulfate, filtered, and concentrated. The residue was dissolved in *N,N*-dimethylformamide (5 mL) and heated at 120 °C for 16 hours. Standard work up and silica gel chromatography using hexanes:ethyl acetate:dichloromethane (3.5:0.5:4) afforded 59 mg (18%) of 3-(5-fluoropyrid-2-yl)-5-(3-allyloxy-5-cyanophenyl)-1,2,4-oxadiazole: ^{1}H NMR ($CDCl_3$), δ (ppm): 8.70 (d, 1H), 8.27 (m, 1H), 8.15 (s, 1H), 8.01 (s, 1H), 7.62 (m, 1H), 7.41 (s, 1H), 6.04 (m, 1H), 5.48 (dd, 1H), 5.34 (dd, 1H), 4.69 (d, 2H).

3-(5-Cyanopyrid-2-yl)-5-(3-cyano-5-propoxyphenyl)-1,2,4-oxadiazole

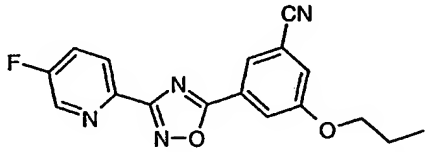
B159



Using the general procedure for the preparation of acid chlorides, 3-cyano-5-propoxybenzoyl chloride was prepared from 3-cyano-5-propoxybenzoic acid (205 mg, 1.0 mmol). A solution of the acid chloride in dichloromethane (2 mL) at 0°C was treated with 5-cyanopyrid-2-ylamidoxime (162 mg, 1.0 mMol) and triethylamine (418 µL, 3.0 mmol) and then stirred at ambient temperature for 1 hour. The reaction mixture was washed with water and saturated brine, dried over anhydrous sodium sulfate, filtered, and concentrated. The residue was dissolved in *N,N*-dimethylformamide (5 mL) and heated at 120 °C for 16 hours. Standard work up and silica gel chromatography using hexanes:ethyl acetate:dichloromethane (3.7:0.3:4) afforded 65 mg (20%) of 3-(5-cyanopyrid-2-yl)-5-(3-cyano-5-propoxyphenyl)-1,2,4-oxadiazole: ^{1}H NMR ($CDCl_3$), δ (ppm): 9.11 (s, 1H), 8.39 (d, 1H), 8.22 (d, 1H), 8.13 (s, 1H), 7.99 (s, 1H), 7.42 (s, 1H), 4.06 (t, 2H), 1.89 (m, 2H), 1.09 (s, 3H).

3-(5-Fluoropyrid-2-yl)-5-(3-cyano-5-propoxyphenyl)-1,2,4-oxadiazole

B160

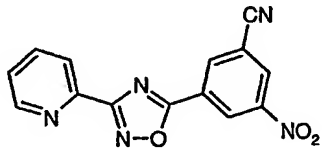


Using the general procedure for the preparation of acid chlorides, 3-cyano-5-propoxybenzoyl chloride was prepared from 3-cyano-5-propoxybenzoic acid (205 mg, 1.0 mmol). A solution of the acid chloride in dichloromethane (2 mL) at 0°C was treated with 5-fluoropyrid-2-ylamidoxime (155 mg, 1.0 mMol) and triethylamine (418 µL, 3.0 mMol) and then stirred at ambient temperature for 1 hour. The reaction mixture was washed with water and saturated brine, dried over anhydrous sodium sulfate, filtered, and concentrated. The residue was dissolved in *N,N*-dimethylformamide (5 mL) and heated at 120 °C for 16 hours. Standard work

up and silica gel chromatography using hexanes:ethyl acetate:dichloromethane (3.7:0.3:4) afforded 120 mg (37%) of 3-(5-fluoropyrid-2-yl)-5-(3-cyano-5-propoxyphenyl)-1,2,4-oxadiazole: ^{1}H NMR ($CDCl_3$), δ (ppm): 8.70 (d, 1H), 8.27 (m, 1H), 8.12 (s, 1H), 7.99 (s, 1H), 7.62 (m, 1H), 7.39 (s, 1H), 4.06 (t, 2H), 1.88 (m, 2H), 1.08 (s, 3H).

3-(2-Pyridyl)-5-(3-cyano-5-nitrophenyl)-1,2,4-oxadiazole

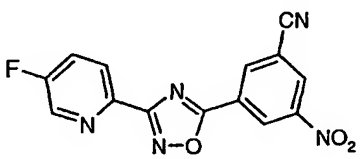
B161



Using the general procedure for the preparation of acid chlorides, 3-cyano-5-nitrobenzoyl chloride was prepared from 3-cyano-5-nitrobenzoic acid (1.0 g, 5.1 mmol). A solution of the acid chloride in dichloromethane (5 mL) at 0°C was treated with pyrid-2-ylamidoxime (700 mg, 5.1 mMol) and triethylamine (2.1 mL, 15.3 mmol) and then stirred at ambient temperature for 1 hour. The reaction mixture was washed with water and saturated brine, dried over anhydrous sodium sulfate, filtered, and concentrated. The residue was dissolved in *N,N*-dimethylformamide (5 mL) and heated at 110 °C for 4 hours. Standard work up and silica gel chromatography using hexanes:ethyl acetate:dichloromethane (3.5:0.5:4) afforded 149 mg (50%) of 3-(2-pyridyl)-5-(3-cyano-5-nitrophenyl)-1,2,4-oxadiazole: ^{1}H NMR ($CDCl_3$), δ (ppm): 9.35 (d, 1H), 8.91 (s, 1H), 8.89 (d, 1H), 8.75 (s,1H), 8.26 (d, 1H), 7.94 (m, 1H), 7.53 (m, 1H).

3-(5-fluoropyrid-2-yl)-5-(3-cyano-5-nitrophenyl)-1,2,4-oxadiazole

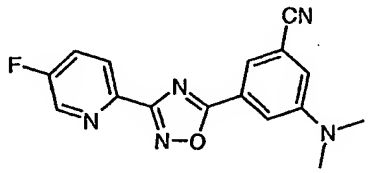
B162



Using the general procedure for the preparation of acid chlorides, 3-cyano-5-nitrobenzoyl chloride was prepared from 3-cyano-5-nitrobenzoic acid (1.0 g, 5.1 mmol). A solution of the acid chloride in dichloromethane (5 mL) at 0°C was treated with 5-fluoropyrid-2-ylamidoxime (791 mg, 5.1 mMol) and triethylamine (2.1 mL, 15.3 mmol) and then stirred at ambient temperature for 1 hour. The reaction mixture was washed with water and saturated brine, dried over anhydrous sodium sulfate, filtered, and concentrated. The residue was dissolved in *N,N*-dimethylformamide (5 mL) and heated at 110 °C for 4 hours. Standard work up and silica gel chromatography using hexanes:ethyl acetate:dichloromethane (3.5:0.5:4) afforded 131 mg (8%) of 3-(5-fluoropyrid-2-yl)-5-(3-cyano-5-nitrophenyl)-1,2,4-oxadiazole: ^{1}H NMR ($CDCl_3$), δ (ppm): 9.34 (s, 1H), 8.89 (s, 1H), 8.74 (d, 2H), 8.30 (m, 1H), 7.66 (m, 1H).

3-(5-fluoropyrid-2-yl)-5-(3-cyano-5-dimethylaminophenyl)-1,2,4-oxadiazole

B163

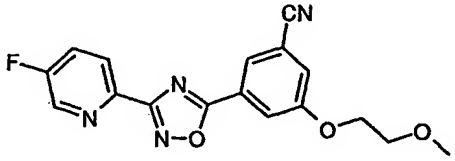


Using the general procedure for the preparation of acid chlorides, 3-cyano-5-dimethylaminobenzoyl chloride was prepared from 3-cyano-5-dimethylaminobenzoic acid (190 mg, 1.0 mmol). A solution of the acid chloride in dichloromethane (3 mL) at 0°C was treated with 5-fluoropyrid-2-ylamidoxime (155 mg, 1.0 mmol) and triethylamine (697 µL, 5.0 mmol) and then stirred at ambient temperature for 1 hour. The reaction mixture was washed with water and saturated brine, dried over anhydrous sodium sulfate, filtered, and concentrated. The residue was dissolved in *N,N*-dimethylformamide (5 mL) and heated at 120 °C for 16 hours. After cooling, water was added to the reaction mixture and then the precipitate was collected and dried. Filtration through silica gel using dichloromethane followed by trituration with dichloromethane afforded 14 mg (5%) of 3-(5-fluoropyrid-2-yl)-5-(3-cyano-5-

dimethylaminophenyl)-1,2,4-oxadiazole: ^{1}H NMR ($CDCl_3$), δ (ppm): 8.70 (d, 1H), 8.27 (m, 1H), 7.81 (s, 1H), 7.70 (s, 1H), 7.62 (m, 1H), 7.08 (s, 1H), 3.11 (s, 6H).

3-(5-fluoropyrid-2-yl)-5-(3-cyano-5-(2-methoxyethoxy)phenyl)-1,2,4-oxadiazole

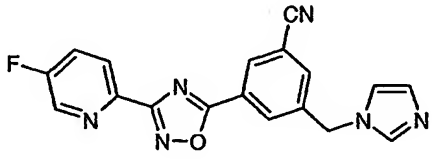
B164



Using the general procedure for the preparation of acid chlorides, 3-cyano-5-(2-methoxyethoxy)benzoyl chloride was prepared from 3-cyano-5-(2-methoxyethoxy)benzoic acid (221 mg, 1.0 mmol). A solution of the acid chloride in dichloromethane (2 mL) at 0°C was treated with 5-fluoropyrid-2-ylamidoxime (155 mg, 1.0 mmol) and triethylamine (418 µL, 3.0 mmol) and then stirred at ambient temperature for 1 hour. The reaction mixture was washed with water and saturated brine, dried over anhydrous sodium sulfate, filtered, and concentrated. The residue was dissolved in *N,N*-dimethylformamide (2 mL) and heated at 120 °C for 16 hours. After cooling, water was added to the reaction mixture and then the precipitate was collected and dried. Silica gel chromatography using 40% ethyl acetate/hexanes followed by trituration with diethyl ether afforded 169 mg (50%) of 3-(5-fluoropyrid-2-yl)-5-(3-cyano-5-(2-methoxyethoxy)phenyl)-1,2,4-oxadiazole: ^{1}H NMR ($CDCl_3$), δ (ppm): 8.70 (d, 1H), 8.27 (m, 1H), 8.15 (s, 1H), 8.03 (s, 1H), 7.62 (m, 1H), 7.44 (s, 1H), 4.27 (t, 2H), 3.81 (t, 2H), 3.48 (s, 3H).

3-(5-fluoropyrid-2-yl)-5-(3-cyano-5-(1H-imidazol-1-ylmethyl)phenyl)-1,2,4-oxadiazole

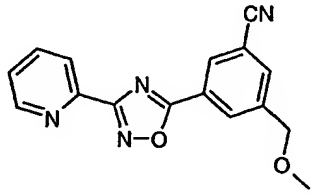
B165



Using the general procedure for the preparation of acid chlorides, 3-cyano-5-(1H-imidazol-1-yl-methyl)benzoyl chloride was prepared from 3-cyano-5-(1H-imidazol-1-yl-methyl)benzoic acid (140 mg, 0.62 mmol). A solution of the acid chloride in dichloromethane (2 mL) at 0°C was treated with 5-fluoropyrid-2-ylamidoxime (96 mg, 0.62 mmol) and triethylamine (258 µL, 1.9 mmol) and then stirred at ambient temperature for 1 hour. The reaction mixture was washed with water and saturated brine, dried over anhydrous sodium sulfate, filtered, and concentrated. The residue was dissolved in *N,N*-dimethylformamide (2 mL) and heated at 120 °C for 16 hours. After cooling, water was added to the reaction mixture and then the precipitate was collected and dried. Silica gel chromatography using 40% ethyl acetate/hexanes followed by trituration with diethyl ether afforded 4 mg (2%) of 3-(5-fluoropyrid-2-yl)-5-(3-cyano-5-(1H-imidazol-1-ylmethyl)phenyl)-1,2,4-oxadiazole: ^{1}H NMR ($CDCl_3$), δ (ppm): 8.71 (d, 1H), 8.53 (s, 1H), 8.33 (s, 1H), 8.28 (m, 1H), 7.63 (m, 3H), 7.21 (s, 1H), 6.97 (s, 1H), 5.30 (s, 2H).

3-(2-Pyridyl)-5-(3-cyano-5-(methoxymethyl)phenyl)-1,2,4-oxadiazole

B166

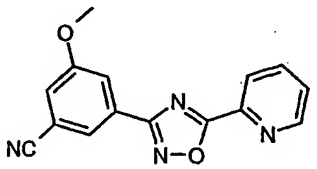


Using the general procedure for the preparation of acid chlorides, 3-cyano-5-(methoxymethyl)benzoyl chloride was prepared from 3-cyano-5-(methoxymethyl)benzoic acid (157 mg, 0.82 mmol). A solution of the acid chloride in dichloromethane (2 mL) at 0°C was treated with pyrid-2-ylamidoxime (113 mg, 0.82 mmol) and triethylamine (343 µL, 2.5 mmol) and then stirred at ambient temperature for 3 hours. The reaction mixture was washed with water and saturated brine, dried over anhydrous sodium sulfate, filtered, and concentrated. The residue was dissolved in *N,N*-dimethylformamide (2 mL) and heated at 120 °C for 16 hours. After cooling, water was added to the reaction mixture and the

precipitate that formed was collected and dried. The solid was dissolved in dichloromethane and silica gel was added to the solution to remove the dark color. The silica gel was then filtered off and the filtrate was concentrated to dryness. Trituration of the residue with diethyl ether afforded 44 mg (18%) of 3-(2-pyridyl)-5-(3-cyano-5-(methoxymethyl)phenyl)-1,2,4-oxadiazole as a white solid: ^{1}H NMR ($CDCl_3$), δ (ppm): 8.87 (d, 1H), 8.50 (s, 2H), 8.23 (d, 1H), 7.94 (m, 1H), 7.89 (s, 1H), 7.50 (m, 1H), 4.59 (s, 2H), 3.49 (s, 3H).

3-(3-cyano-5-methoxyphenyl)-5-(2-pyridyl)-1,2,4-oxadiazole

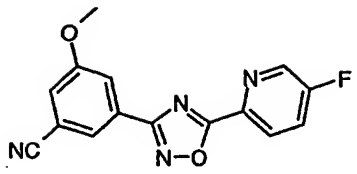
B167



Using the general procedure for the preparation of acid chlorides, picolinoyl chloride was prepared from picolinic acid (300 mg, 2.4 mmol). A solution of the acid chloride in dichloromethane (2 mL) at 0°C was treated with of 3-cyano-5-methoxyphenyl-amidoxime (100 mg, 0.52 mmol) and triethylamine (1.0 mL, 7.2 mmol) and then stirred at ambient temperature for 1 hour. The reaction mixture was washed with water and saturated brine, dried over anhydrous sodium sulfate, filtered, and concentrated. The residue was dissolved in *N,N*-dimethylformamide (2 mL) and heated at 120 °C for 16 hours. Standard work up and silica gel chromatography using 10-20% ethyl acetate/hexanes followed by trituration with hexanes afforded 10 mg (7%) of 3-(3-cyano-5-methoxyphenyl)-5-(2-pyridyl)-1,2,4-oxadiazole: ^{1}H NMR ($CDCl_3$), δ (ppm): 8.90 (d, 1H), 8.32 (d, 1H), 8.13 (s, 1H), 7.98 (m, 2H), 7.58 (dd, 1H), 7.31 (s, 1H), 3.94 (s, 3H).

3-(3-Cyano-5-methoxyphenyl)-5-(5-fluoropyrid-2-yl)-1,2,4-oxadiazole

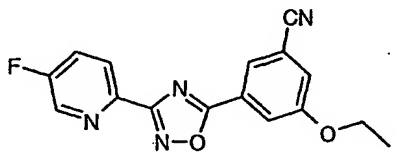
B168



Using the general procedure for the preparation of acid chlorides, 5-fluoro-picolinoyl chloride was prepared from 5-fluoro-picolinic acid hydrochloride (177 mg, 1.0 mmol). A solution of the acid chloride in dichloromethane (2 mL) at 0°C was treated with of 3-cyano-5-methoxyphenyl-amidoxime (100 mg, 0.52 mmol) and triethylamine (418 µL, 3.0 mmol) and then stirred at ambient temperature for 1 hour. The reaction mixture was washed with water and saturated brine, dried over anhydrous sodium sulfate, filtered, and concentrated. The residue was dissolved in *N,N*-dimethylformamide (2 mL) and heated at 120 °C for 16 hours. Standard work up and silica gel chromatography using 10-20% ethyl acetate/hexanes followed by trituration with diethyl ether/hexanes afforded 20 mg (19%) of 3-(3-cyano-5-methoxyphenyl)-5-(5-fluoropyrid-2-yl)-1,2,4-oxadiazole: ^{1}H NMR ($CDCl_3$), δ (ppm): 8.75 (s, 1H), 8.40 (dd, 1H), 8.13 (s, 1H), 7.96 (s, 1H), 7.68 (m, 1H), 7.38 (s, 1H), 3.94 (s, 3H).

3-(5-fluoropyrid-2-yl)-5-(3-cyano-5-ethoxyphenyl)-1,2,4-oxadiazole

B169

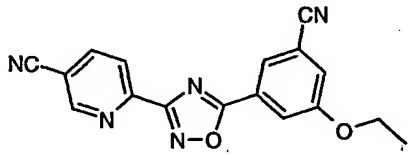


Using the general procedure for the preparation of acid chlorides, 3-cyano-5-ethoxybenzoyl chloride was prepared from 3-cyano-5-ethoxybenzoic acid (145 mg, 0.75 mmol). A solution of the acid chloride in dichloromethane (2 mL) at 0°C was treated with 5-fluoropyrid-2-ylamidoxime (117 mg, 0.75 mmol) and triethylamine (315 µL, 2.26 mmol) and then stirred at ambient temperature for 1 hour. The reaction mixture was washed with water and saturated brine, dried over anhydrous sodium sulfate, filtered, and concentrated. The residue was dissolved in *N,N*-dimethylformamide (2 mL) and heated at 120 °C for 16 hours. Standard work up

and silica gel chromatography using 5-20% ethyl acetate/hexanes followed by trituration with diethyl ether afforded 54 mg (23%) of 3-(5-fluoropyrid-2-yl)-5-(3-cyano-5-ethoxyphenyl)-1,2,4-oxadiazole: ^{1}H NMR ($CDCl_3$), δ (ppm): 8.69 (d, 1H), 8.26 (dd, 1H), 8.12 (s, 1H), 7.97 (s, 1H), 7.60 (m, 1H), 7.38 (s, 1H), 4.16 (q, 2H), 1.49 (t, 3H).

3-(5-Cyanopyrid-2-yl)-5-(3-cyano-5-ethoxyphenyl)-1,2,4-oxadiazole

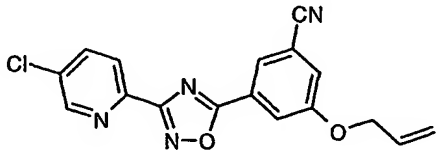
B170



Using the general procedure for the preparation of acid chlorides, 3-cyano-5-ethoxybenzoyl chloride was prepared from 3-cyano-5-ethoxybenzoic acid (145 mg, 0.75 mmol). A solution of the acid chloride in dichloromethane (2 mL) at 0°C was treated with 5-cyanopyrid-2-ylamidoxime (122 mg, 0.75 mmol) and triethylamine (315 μL, 2.3 mmol) and then stirred at ambient temperature for 1 hour. The reaction mixture was washed with water and saturated brine, dried over anhydrous sodium sulfate, filtered, and concentrated. The residue was dissolved in *N,N*-dimethylformamide (2 mL) and heated at 120 °C for 16 hours. Standard work up and silica gel chromatography using 5-20% ethyl acetate/hexanes followed by trituration with diethyl ether afforded 85 mg (35%) of 3-(5-cyanopyrid-2-yl)-5-(3-cyano-5-ethoxyphenyl)-1,2,4-oxadiazole: ^{1}H NMR ($CDCl_3$), δ (ppm): 9.11 (s, 1H), 8.38 (d, 1H), 8.20 (dd, 1H), 8.13 (s, 1H), 7.98 (d, 1H), 7.40 (s, 1H), 4.17 (q, 2H), 1.50 (t, 3H).

3-(5-Chloropyrid-2-yl)-5-(3-allyloxoy-5-cyanophenyl)-1,2,4-oxadiazole

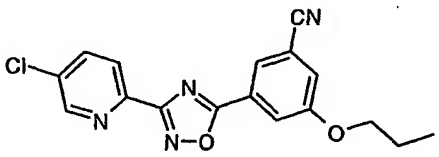
B171



Using the general procedure for the preparation of acid chlorides, 3-allyloxy-5-cyanobenzoyl chloride was prepared from 3-allyloxy-5-cyanobenzoic acid (279 mg, 1.4 mmol). A solution of the acid chloride in dichloromethane (3 mL) at 0°C was treated with 5-chloropyrid-2-ylamidoxime (231 mg, 1.4 mmol) and triethylamine (574 µL, 4.1 mmol) and then stirred at ambient temperature for 1 hour. The reaction mixture was washed with water and saturated brine, dried over anhydrous sodium sulfate, filtered, and concentrated. The residue was dissolved in *N,N*-dimethylformamide (3 mL) and heated at 120 °C for 16 hours. Standard work up and silica gel chromatography using 5-20% ethyl acetate/hexanes followed by trituration with diethyl ether afforded 192 mg (42%) of 3-(5-chloropyrid-2-yl)-5-(3-allyloxy-5-cyanophenyl)-1,2,4-oxadiazole: ^{1}H NMR ($CDCl_3$), δ (ppm): 8.79 (d, 1H), 8.18 (d, 1H), 8.14 (m, 1H), 7.99 (s, 1H), 7.88 (d, 1H), 7.40 (s, 1H), 6.07 (m, 1H), 5.40 (m, 2H), 4.67 (d, 2H).

3-(5-Chloropyrid-2-yl)-5-(3-cyano-5-propoxyphenyl)-1,2,4-oxadiazole

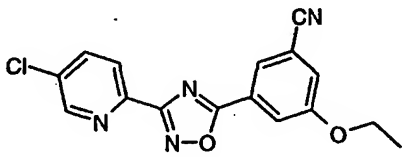
B172



Using the general procedure for the preparation of acid chlorides, 3-cyano-5-propoxybenzoyl chloride was prepared from 3-cyano-5-propoxybenzoic acid (93 mg, 0.45 mmol). A solution of the acid chloride in dichloromethane (2 mL) at 0°C was treated with 5-chloropyrid-2-ylamidoxime (76 mg, 0.45 mmol) and triethylamine (188 µL, 1.4 mmol) and then stirred at ambient temperature for 1 hour. The reaction mixture was washed with water and saturated brine, dried over anhydrous sodium sulfate, filtered, and concentrated. The residue was dissolved in *N,N*-dimethylformamide (2 mL) and heated at 120 °C for 16 hours. Standard work up and silica gel chromatography using 10% ethyl acetate/hexanes afforded 7 mg (4%) of 3-(5-chloropyrid-2-yl)-5-(3-cyano-5-propoxyphenyl)-1,2,4-oxadiazole: ^{1}H NMR ($CDCl_3$), δ (ppm): 8.80 (d, 1H), 8.18 (d, 1H), 8.11 (s, 1H), 7.98 (s, 1H), 7.88 (dd, 1H), 7.39 (s, 1H), 4.05 (t, 2H), 1.87 (m, 2H), 1.08 (t, 3H).

3-(5-Chloropyrid-2-yl)-5-(3-cyano-5-ethoxyphenyl)-1,2,4-oxadiazole

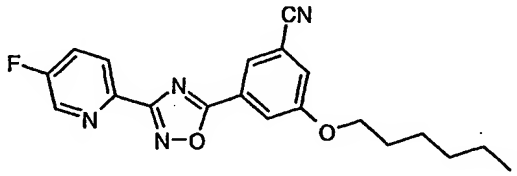
B173



Using the general procedure for the preparation of acid chlorides, 3-cyano-5-ethoxybenzoyl chloride was prepared from 3-cyano-5-ethoxybenzoic acid (189 mg, 0.94 mmol). A solution of the acid chloride in dichloromethane (2 mL) at 0°C was treated with 5-chloropyrid-2-ylamidoxime (159 mg, 0.94 mmol) and triethylamine (399 µL, 2.9 mmol) and then stirred at ambient temperature for 1 hour. The reaction mixture was washed with water and saturated brine, dried over anhydrous sodium sulfate, filtered, and concentrated. The residue was dissolved in *N,N*-dimethylformamide (2 mL) and heated at 120 °C for 16 hours. After cooling, water was added to the reaction mixture and then the precipitate was collected and dried. Filtration through silica gel using dichloromethane followed by trituration with diethyl ether afforded 193 mg (62%) of 3-(5-chloropyrid-2-yl)-5-(3-cyano-5-ethoxyphenyl)-1,2,4-oxadiazole: ^{1}H NMR ($CDCl_3$), δ (ppm): 8.79 (d, 1H), 8.18 (d, 1H), 8.12 (s, 1H), 7.97 (s, 1H), 7.88 (dd, 1H), 7.38 (s, 1H), 4.16 (q, 2H), 1.49 (t, 3H).

3-(5-Fluoropyrid-2-yl)-5-(3-cyano-5-hexyloxyphenyl)-1,2,4-oxadiazole

B174

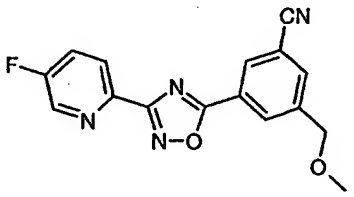


Using the general procedure for the preparation of acid chlorides, 3-cyano-5-hexyloxybenzoyl chloride was prepared from 3-cyano-5-hexyloxybenzoic acid (247 mg, 0.96 mmol). A solution of the acid chloride in dichloromethane (2 mL) at 0°C was treated with 5-fluoropyrid-2-ylamidoxime (149 mg, 0.96 mmol) and

triethylamine (399 µL, 2.9 mmol) and then stirred at ambient temperature for 1 hour. The reaction mixture was washed with water and saturated brine, dried over anhydrous sodium sulfate, filtered, and concentrated. The residue was dissolved in *N,N*-dimethylformamide (2 mL) and heated at 120 °C for 16 hours. Standard work up and filtration through silica gel using dichloromethane followed by trituration with diethyl ether afforded 75 mg (21%) of 3-(5-fluoropyrid-2-yl)-5-(3-cyano-5-hexyloxyphenyl)-1,2,4-oxadiazole: ^{1}H NMR ($CDCl_3$), δ (ppm): 8.69 (d, 1H), 8.27 (dd, 1H), 8.12 (s, 1H), 7.98 (s, 1H), 7.62 (m, 1H), 7.39 (s, 1H), 4.09 (t, 2H), 1.84 (m, 2H), 1.49 (m, 2H), 1.37 (m, 4H), 0.93 (t, 3H).

3-(5-Fluoropyrid-2-yl)-5-(3-cyano-5-(methoxymethyl)phenyl)-1,2,4-oxadiazole

B175

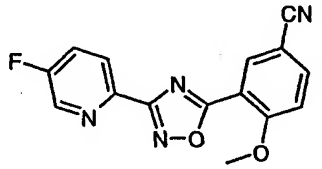


Using the general procedure for the preparation of acid chlorides, 3-cyano-5-(methoxymethyl)benzoyl chloride was prepared from 3-cyano-5-(methoxymethyl)benzoic acid (143 mg, 0.75 mmol). A solution of the acid chloride in dichloromethane (2 mL) at 0°C was treated with 5-fluoropyrid-2-ylamidoxime (123 mg, 0.75 mmol) and triethylamine (313 µL, 2.2 mmol) and then stirred at ambient temperature for 3 hours. The reaction mixture was washed with water and saturated brine, dried over anhydrous sodium sulfate, filtered, and concentrated. The residue was dissolved in *N,N*-dimethylformamide (2 mL) and heated at 120 °C for 16 hours. After cooling, water was added to the reaction mixture and the precipitate that formed was collected and dried. The solid was dissolved in dichloromethane and silica gel was added to the solution to remove the dark color. The silica gel was then filtered off and the filtrate was concentrated to dryness. Trituration of the residue with diethyl ether afforded 60 mg (25%) of 3-(5-fluoropyrid-2-yl)-5-(3-cyano-5-(methoxymethyl)phenyl)-1,2,4-oxadiazole as a

white solid: ^{1}H NMR ($CDCl_3$), δ (ppm): 8.69 (d, 1H), 8.48 (s, 2H), 8.27 (dd, 1H), 7.89 (s, 1H), 7.62 (m, 1H), 4.59 (s, 2H), 3.49 (s, 3H).

3-(5-Fluoro-pyrid-2-yl)-5-(5-cyano-2-methoxyphenyl)-1,2,4-oxadiazole

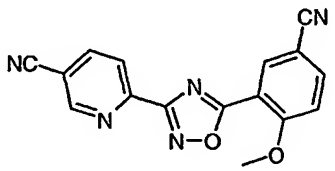
B176



A mixture of 5-cyano-2-methoxybenzoic acid (1.77mg, 1 mmol) in dichloromethane (2 mL) was treated with 2M oxalyl chloride (2 ml, 4 mmol, dichloromethane) and 1 drops of *N,N*-dimethylformamide. The mixture was stirred 2 hours at room temperature. The solvent and excess reagent were removed *in vacuo*. The residue was treated with 5-fluoropyrid-2-ylamidoxime (155 mg, 1 mmol) and triethylamine (404 mg, 4 mmol) in dichloromethane (10 mL). The mixture was then heated in dimethylformamide (1 mL) for 3 hours at 120 °C. Standard work up, afforded 75 mg (25.3%) of 3-(5-Fluoro-pyrid-2-yl)-5-(5-cyano-2-methoxyphenyl)-1,2,4-oxadiazole. ^{1}H NMR ($CDCl_3$), δ (ppm): 8.69 (d, 1H), 8.59 (d, 1H), 8.26 (dd, 1H), 7.85 (dd, 1H), 7.60 (m, 1H), 7.19 (d, 1H), 4.10 (s, 3H).

5-(5-Cyano-2-methoxyphenyl)- 3-(5-cyano-pyrid-2-yl)-1,2,4-oxadiazole

B177

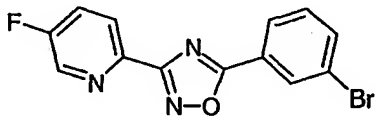


A mixture of 5-cyano-2-methoxybenzoic acid (1.77mg, 1 mmol) in dichloromethane (2 mL) was treated with 2M oxalyl chloride (2 ml, 4 mmol, dichloromethane) and 1 drops of *N,N*-dimethylformamide. The mixture was stirred 2 hours at room temperature. The solvent and excess reagent were removed *in vacuo*. The residue was treated with 5-cyanopyrid-2-ylamidoxime (162 mg, 1

mmol) and triethylamine (404 mg, 4 mmol) in dichloromethane (2 mL). The mixture was then heated in dimethylformamide (1 mL) for 3 hours at 120 °C. Standard work up, afforded 67 mg (22%) of 5-(5-cyano-2-methoxyphenyl)-3-(5-cyano-pyrid-2-yl)-1,2,4-oxadiazole. ^{1}H NMR ($CDCl_3$), δ (ppm): 9.10 (s, 1H), 8.58 (d, 1H), 8.37 (dd, 1H), 8.19 (dd, 1H), 7.86 (dd, 1H), 7.20 (d, 1H), 4.11 (s, 3H).

3-(5-Fluoro-pyrid-2-yl)-5-(3-bromophenyl)-1,2,4-oxadiazole

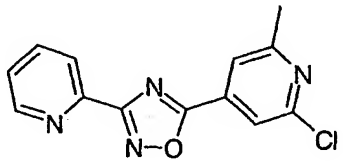
B178



To the dichloromethane solution (2 mL) of 5-fluoropyrid-2-ylamidoxime (155 mg, 1 mmol) and triethylamine (404 mg, 4 mmol), 3-bromobenzoyl chloride (1.77mg, 1 mmol) was added at room temperature. The mixture was then heated in dimethylformamide (1 mL) for 40 minutes at 120～130 °C. Standard work up, afforded 225 mg (70.3%) of 3-(5-Fluoro-pyrid-2-yl)-5-(3-bromophenyl)-1,2,4-oxadiazole.

5-(3-Chloro-5-methyl-pyrid-4-yl)-3-(2-pyridyl)-1,2,4-oxadiazole

B179

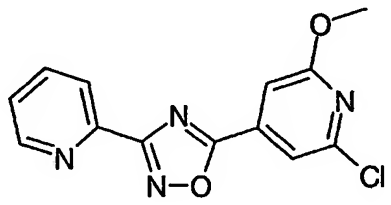


A mixture of 2-chloro-6-methylisonicotinic acid (1.71 g, 10 mmol) in dichloromethane (15 mL) was treated with 2M oxalyl chloride (15 ml, 30 mmol, dichloromethane) and 3 drops of *N,N*-dimethylformamide. The mixture was stirred 2 hours at room temperature. The solvent and excess reagent were removed *in vacuo*. The residue was treated with 2-pyridylamidoxime (1.37 g, 10 mmol) and triethylamine (3.03 g, 30 mmol) in dichloromethane (15 mL). The mixture was then heated in dimethylformamide (10 mL) for 1 hours at 120 °C. Standard work

up, afforded 1.63 g (60%) of 5-(3-chloro-5-methyl-pyrid-4-yl)-3-(2-pyridyl)-1,2,4-oxadiazole.

5-(3-Chloro-5-methoxy-pyrid-4-yl)-3-(2-pyridyl)-1,2,4-oxadiazole

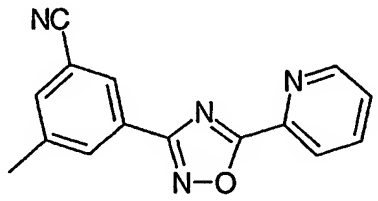
B180



A mixture of 2-chloro-6-methoxyisonicotinic acid (1.87 g, 10 mmol) in dichloromethane (15 mL) was treated with 2M oxalyl chloride (15 ml, 30 mmol, dichloromethane) and 3 drops of *N,N*-dimethylformamide. The mixture was stirred 2 hours at room temperature. The solvent and excess reagent were removed *in vacuo*. The residue was treated with 2-pyridylamidoxime (1.37 g, 10 mmol) and triethylamine (3.03 g, 30 mmol) in dichloromethane (15 mL). The mixture was then heated in dimethylformamide (10 mL) for 1 hours at 120 °C. Standard work up, afforded 1.63 g (60%) of 3-(2-pyridyl)-5-(3-chloro-5-methoxy-pyrid-4-yl)-1,2,4-oxadiazole.

3-(3-Cyano-5-methylphenyl)-5-(2-pyridyl)-1,2,4-oxadiazole

B181

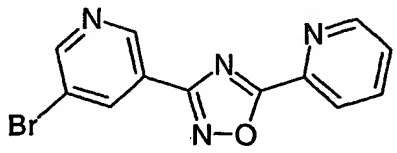


A mixture of picolinic acid (123 mg, 1 mmol) in dichloromethane (2 mL) was treated with 2M oxalyl chloride (2 ml, 4 mmol, dichloromethane). The mixture was stirred 2 hours at room temperature. The solvent and excess reagent were removed *in vacuo*. The residue was treated with 3-cyano-5-methylphenyl-amidoxime (80 mg, 0.457 mmol) and triethylamine (303 mg, 3 mmol) in

dichloromethane (2 mL). The mixture was then heated in dimethylformamide (2 mL) for 1 hours at 120 °C. Standard work up, afforded 5.8 mg (4.8%) of 3-(3-cyano-5-methylphenyl)-5-(2-pyridyl)-1,2,4-oxadiazole. ^{1}H-NMR ($CDCl_3$), δ (ppm): 8.89 (d, 1H), 8.30 (s,m, 3H), 7.96 (dt, 1H), 7.60 (s,dd, 2H), 2.50 (s, 3H).

3-(5-Bromo-pyrid-3-yl)-5-(2-pyridyl)-1,2,4-oxadiazole

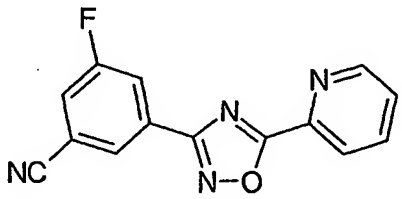
B182



A mixture of picolinic acid (123 mg, 1 mmol) in dichloromethane (2 mL) was treated with 2M oxalyl chloride (2 ml, 4 mmol, dichloromethane). The mixture was stirred 2 hours at room temperature. The solvent and excess reagent were removed *in vacuo*. The residue was treated with 5-bromopyrid-3-ylamidoxime (216 mg, 1 mmol) and triethylamine (303 mg, 3 mmol) in dichloromethane (2 mL). The mixture was then heated in dimethylformamide (2 mL) for 1 hours at 120 °C. Standard work up, afforded 103 mg (34%) of 3-(5-bromo-pyrid-3-yl)-5-(2-pyridyl)-1,2,4-oxadiazole. ^{1}H-NMR ($CDCl_3$), δ (ppm): 9.36 (d, 1H), 8.90 (d, 1H), 8.84 (d, 1H), 8.68 (t, 1H), 8.32 (d, 1H), 7.98 (dt, 1H), 7.58 (dd, 1H).

3-(3-Cyano-5-fluorophenyl)-5-(2-pyridyl)-1,2,4-oxadiazole

B183

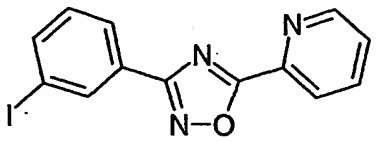


A mixture of picolinic acid (184.6 mg, 1.5 mmol) in dichloromethane (2 mL) was treated with 2M oxalyl chloride (3 ml, 6 mmol, dichloromethane). The mixture was stirred overnight at room temperature. The solvent and excess reagent were removed *in vacuo*. The residue was treated with 3-cyano-5-fluorophenyl-

amidoxime (100 mg, 0.558 mmol) and triethylamine (558 mg, 5.58 mmol) in dichloromethane (2 mL). The mixture was then heated in dimethylformamide (1 mL) for 1 hours at 120 °C. Standard work up, afforded 43 mg (28.9%) of 3-(5-cyano-3-fluorophenyl)-5-(2-pyridyl)-1,2,4-oxadiazole. ^{1}H-NMR ($CDCl_3$), δ (ppm): 8.89 (d, 1H), 8.34 (s,d, 3H), 8.10 (d, 1H), 7.59 (m, 2H).

3-(3-Iodophenyl)-5-(2-pyridyl)-1,2,4-oxadiazole

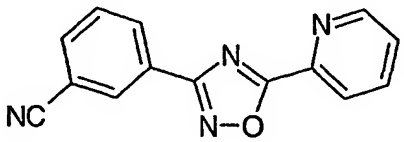
B184



A mixture of picolinic acid (300 mg, 2.4 mmol) in dichloromethane (2 mL) was treated with 2M oxalyl chloride (2 ml, 4 mmol, dichloromethane). The mixture was stirred 5 hours at room temperature. The solvent and excess reagent were removed *in vacuo*. The residue was treated with 3-iodophenyl-amidoxime (263 mg, 1 mmol) and triethylamine (303 mg, 3 mmol) in dichloromethane (2 mL). The mixture was then heated in dimethylformamide (2 mL) for 1 hours at 120~130 °C. Standard work up, afforded 64.5 mg (18.5%) of 3-(3-iodophenyl)-5-(2-pyridyl)-1,2,4-oxadiazole. ^{1}H-NMR ($CDCl_3$), δ (ppm): 8.88 (d, 1H), 8.61 (s, 1H), 8.31 (d, 1H), 8.20 (d, 1H), 7.96 (t, 1H), 7.87 (d, 1H), 7.56 (m, 1H), 7.25 (m, 1H).

3-(3-Cyanophenyl)-5-(2-pyridyl)-1,2,4-oxadiazole

B186

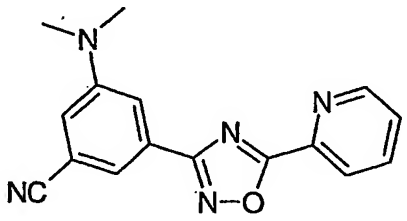


A mixture of picolinic acid (300 mg, 2.4 mmol) in dichloromethane (2 mL) was treated with 2M oxalyl chloride (2 ml, 4 mmol, dichloromethane). The mixture was stirred 5 hours at room temperature. The solvent and excess reagent were removed *in vacuo*. The residue was treated with 3-iodophenyl-amidoxime

(161 mg, 1 mmol) and triethylamine (303 mg, 3 mmol) in dichloromethane (2 mL). The mixture was then heated in dimethylformamide (2 mL) for 1 hours at 120~130 °C. Standard work up, afforded 21.1 mg (8.5%) of 3-(3-cyanophenyl)-5-(2-pyridyl)-1,2,4-oxadiazole. ^{1}H-NMR ($CDCl_3$), δ (ppm): 8.89 (d, 1H), 8.55 (s, 1H), 8.47 (d, 1H), 8.32 (d, 1H), 7.97 (t, 1H), 7.82 (d, 1H), 7.65 (t, 1H), 7.58 (m, 1H).

3-(3-Cyano-5-dimethylamino-phenyl)-5-(2-pyridyl)-1,2,4-oxadiazole

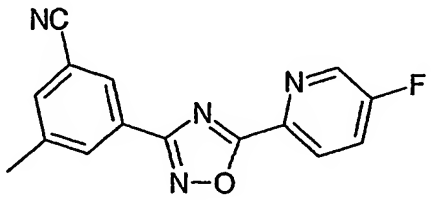
B187



A mixture of picolinic acid (300 mg, 2.4 mmol) in dichloromethane (2 mL) was treated with 2M oxalyl chloride (2 ml, 4 mmol, dichloromethane). The mixture was stirred 5 hours at room temperature. The solvent and excess reagent were removed *in vacuo*. The residue was treated with 3-cyano-5-dimethylaminophenyl-amidoxime (100 mg, 0.5 mmol) and triethylamine (303 mg, 3 mmol) in dichloromethane (2 mL). The mixture was then heated in dimethylformamide (2 mL) for 1 hours at 120~130 °C. Standard work up, afforded 11.8 mg (8.1%) of 3-(3-cyano-5-dimethylamino-phenyl)-5-(2-pyridyl)-1,2,4-oxadiazole. ^{1}H-NMR ($CDCl_3$), δ (ppm): 8.88 (d, 1H), 8.32 (d, 1H), 7.97 (t, 1H), 7.81 (s, 1H), 7.69 (s, 1H), 7.57 (m, 1H), 7.01 (s, 1H), 3.08 (s, 6H).

3-(3-Cyano-5-methylphenyl)-5-(5-fluoro-pyrid-2-yl)-1,2,4-oxadiazole

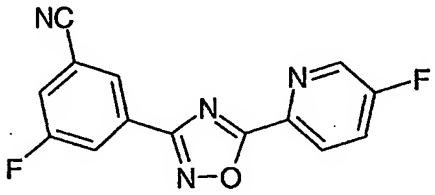
B188



A mixture of 5-fluoro-picolinic acid hydrochloride (177 mg, 1 mmol) in dichloromethane (2 mL) was treated with 2M oxalyl chloride (2 ml, 4 mmol, dichloromethane). The mixture was stirred 2 hours at room temperature. The solvent and excess reagent were removed *in vacuo*. The residue was treated with 3-cyano-5-methylphenyl-amidoxime (90 mg, 0.5 mmol) and triethylamine (303 mg, 3 mmol) in dichloromethane (2 mL). The mixture was then heated in dimethylformamide (2 mL) for 1 hours at 120 °C. Standard work up, afforded 37.4 mg (26.7%) of 3-(3-cyano-5-methylphenyl)-5-(5-fluoro-pyrid-2-yl)-1,2,4-oxadiazole. ^{1}H-NMR ($CDCl_3$), δ (ppm): 8.73 (d, 1H), 8.36 (m, 1H), 8.32 (s, 1H), 8.27 (s, 1H), 7.69 (m, 1H), 7.62 (s, 1H), 2.50 (s, 3H).

3-(3-Cyano-5-fluorophenyl)-5-(5-fluoro-pyrid-2-yl)-1,2,4-oxadiazole

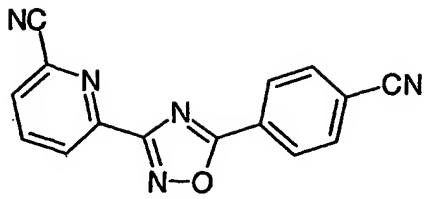
B189



A mixture of 5-fluoro-picolinic acid hydrochloride (177 mg, 1 mmol) in dichloromethane (2 mL) was treated with 2M oxalyl chloride (2 ml, 4 mmol, dichloromethane). The mixture was stirred 2 hours at room temperature. The solvent and excess reagent were removed *in vacuo*. The residue was treated with 3-cyano-5-fluorophenyl-amidoxime (120 mg, 0.67 mmol) and triethylamine (303 mg, 3 mmol) in dichloromethane (2 mL). The mixture was then heated in dimethylformamide (2 mL) for 1 hours at 120 °C. Standard work up, afforded 33 mg (17.3%) of 3-(3-cyano-5-fluorophenyl)-5-(5-fluoro-pyrid-2-yl)-1,2,4-oxadiazole. ^{1}H-NMR ($CDCl_3$), δ (ppm): 8.73 (d, 1H), 8.36 (m, 2H), 8.18 (dd, 1H), 7.69 (dt, 1H), 7.53 (d, 1H).

5-(4-Cyanophenyl)-3-(6-cyano-pyrid-2-yl)-1,2,4-oxadiazole

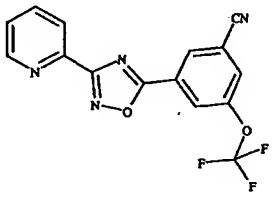
B190



To a dichloromethane solution (1 mL) of 6-cyanopyrid-2-ylamidoxime (81 mg, 0.5 mmol) and triethylamine (202 mg, 2 mmol), 4-cyanobenzoyl chloride (91 mg, 0.55 mmol) was added at room temperature. The mixture was then heated in dimethylformamide (1 mL) for 2 hours at 120~130 °C. Standard work up, afforded 63.4 mg (46.4%) of 5-(4-cyanophenyl)-3-(6-cyano-pyrid-2-yl)-1,2,4-oxadiazole. ^{1}H-NMR ($CDCl_3$), δ (ppm): 8.24 (m, 3H), 8.06 (t, 1H), 7.92 (d, 3H).

5-(3-Cyano-5-trifluoromethoxyphenyl)-3-(2-pyridyl)-1,2,4-oxadiazole

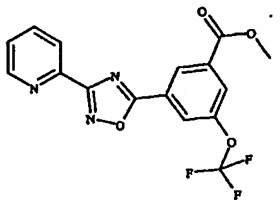
B191



A mixture of 3-cyano-5-trifluoromethoxybenzoic acid, which 3-[imino(methoxy)methyl]-5-trifluoromethoxybenzoic acid (3:1, 50 mg, 0.2165mmoles) in dichloromethane (1 mL) was treated with 2M oxalyl chloride (0.433 ml, 0.866 mmol, dichloromethane). The mixture was stirred 3 hours at room temperature. The solvent and excess reagent were removed *in vacuo*. The residue was treated with 2-pyridyl-amidoxime (29.7 mg, 0.216 mmol) and triethylamine (87 mg, 0.866 mmol) in dichloromethane (1 mL). The mixture was then heated in dimethylformamide (0.5 mL) for 3 hours at 120 °C. Standard work up, purified by prep HPLC (C18 column, CH_3CN:H_2O = 60:40), afforded 3.2 mg (4.5%) of 5-(3-Cyano-5-trifluoromethoxyphenyl)-3-(2-pyridyl)-1,2,4-oxadiazole [^{1}H-NMR ($CDCl_3$), δ (ppm): 8.86 (w, 1H), 8.56 (s, 1H), 8.40 (s, 1H), 8.24 (d, 1H), 7.92 (t, 1H), 7.72 (s, 1H), 7.73 (m, 1H)]

5-(3-methoxycarbonyl-5-trifluoromethoxyphenyl)-3-(2-pyridyl)-1,2,4-oxadiazole

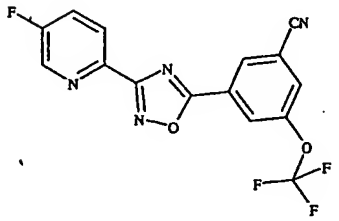
B192



A mixture of 3-cyano-5-trifluoromethoxybenzoic acid, which 3-[imino(methoxy)methyl]-5-trifluoromethoxybenzoic acid (3:1, 50 mg, 0.2165mmoles) in dichloromethane (1 mL) was treated with 2M oxalyl chloride (0.433 ml, 0.866 mmol, dichloromethane). The mixture was stirred 3 hours at room temperature. The solvent and excess reagent were removed *in vacuo*. The residue was treated with 2-pyridyl-amidoxime (29.7 mg, 0.216 mmol) and triethylamine (87 mg, 0.866 mmol) in dichloromethane (1 mL). The mixture was then heated in dimethylformamide (0.5 mL) for 3 hours at 120 °C. Standard work up, purified by prep HPLC (C18 column, $CH_3CN:H_2O$ = 60:40), afforded 1.2 mg (1.5%) of 5-(3-methoxycarbonyl-5-trifluoromethoxyphenyl)-3-(2-pyridyl)-1,2,4-oxadiazole [^{1}H-NMR ($CDCl_3$), δ (ppm): 8.86 (d, w, 2H), 8.36 (s, 1H), 8.25 (d, 1H), 8.15 (s, 1H), 7.90 (t, 1H), 7.51 (m, 1H), 4.01 (s, 3H)].

5-(3-Cyano-5-trifluoromethoxyphenyl)-3-(5-fluoro-pyrid-2-yl)-1,2,4-oxadiazole

B193

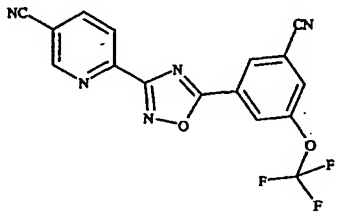


A mixture of 3-cyano-5-trifluoromethoxybenzoic acid, which contained 3-[imino(methoxy)methyl]-5-trifluoromethoxybenzoic acid (3:1, 50 mg, 0.2165mmoles) in dichloromethane (1 mL) was treated with 2M oxalyl chloride (0.433 ml, 0.866 mmol, dichloromethane). The mixture was stirred 3 hours at

room temperature. The solvent and excess reagent were removed *in vacuo*. The residue was treated with 5-fluoropyrid-2-ylamidoxime (33.6 mg, 0.216 mmol) and triethylamine (87 mg, 0.866 mmol) in dichloromethane (1 mL). The mixture was then heated in dimethylformamide (0.5 mL) for 3 hours at 120 °C. Standard work up, purified by prep HPLC (C18 column, CH3CN:H2O = 60:40), afforded 14.9 mg (19.6%) of 5-(3-cyano-5-trifluoromethoxyphenyl)-3-(5-fluoropyrid-2-yl)-1,2,4-oxadiazole. ^{1}H-NMR ($CDCl_3$), δ (ppm): 8.72 (s, 1H), 8.56 (s, 1H), 8.39 (s, 1H), 8.25 (m, 1H), 7.78 (s, 1H), 7.61 (m, 1H).

3-(5-Cyano-pyrid-2-yl)-5-(3-cyano-5-trifluoromethoxyphenyl)-1,2,4-oxadiazole

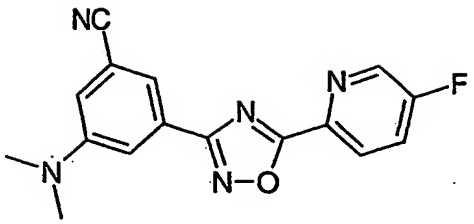
B194



A mixture of 3-cyano-5-trifluoromethoxybenzoic acid, which 3-[imino(methoxy)methyl]-5-trifluoromethoxybenzoic acid (3:1, 50 mg, 0.2165mmoles) in dichloromethane (1 mL) was treated with 2M oxalyl chloride (0.433 ml, 0.866 mmol, dichloromethane). The mixture was stirred 3 hours at room temperature. The solvent and excess reagent were removed *in vacuo*. The residue was treated with 5-cyanopyrid-2-ylamidoxime (33.6 mg, 0.216 mmol) and triethylamine (87 mg, 0.866 mmol) in dichloromethane (1 mL). The mixture was then heated in dimethylformamide (0.5 mL) for 3 hours at 120 °C. Standard work up, purified by prep HPLC (C18 column, CH3CN:H2O = 60:40), afforded 18 mg (22.2%) of 5-(3-cyano-5-trifluoromethoxyphenyl)-3-(5-fluoropyrid-2-yl)-1,2,4-oxadiazole. ^{1}H-NMR ($CDCl_3$), δ (ppm): 9.12 (d, 1H), 8.50 (s, 1H), 8.38 (s, d, 2H), 8.20 (d, 1H), 7.79 (s, 1H).

3-(3-Cyano-5-dimethylaminophenyl)-5-(5-fluoro-pyrid-2-yl)-1,2,4-oxadiazole

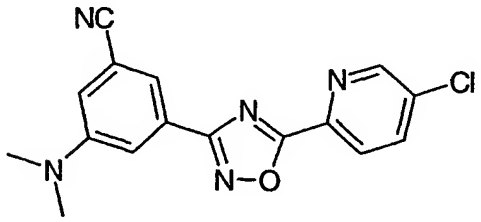
B195



A mixture of 5-fluoro-picolinic acid acid (177.5 mg, 1 mmol) in dichloromethane (2 mL) was treated with 2M oxalyl chloride (2 ml, 4 mmol, dichloromethane). The mixture was stirred 2 hours at room temperature. The solvent and excess reagent were removed *in vacuo*. The residue was treated with 3-cyano-5-dimethylaminophenyl-amidoxime (102 mg, 0.5 mmol) and triethylamine (404 mg, 4 mmol) in dichloromethane (2 mL). The mixture was then heated in dimethylformamide (1 mL) for 1 hours at 130 °C. Standard work up, afforded 24 mg (15.5%) of 3-(3-cyano-5-dimethyaminophenyl)-5-(5-fluoro-pyrid-2-yl)-1,2,4-oxadiazole. ^{1}H-NMR ($CDCl_3$), δ (ppm): 8.72 (d, 1H), 8.37 (dd, 1H), 7.81 (s, 1H), 7.68 (dt, 2H), 7.02 (d, 1H), 3.10 (s, 6H).

5-(5-Chloro-pyrid-2-yl)-3-(3-cyano-5-dimethylaminophenyl)-1,2,4-oxadiazole

B196

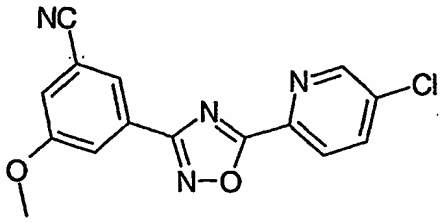


A mixture of 5-chloro-picolinic acid hydrochloride (72 mg, 0.4 mmol) in dichloromethane (2 mL) was treated with 2M oxalyl chloride (0.8 ml, 1.6 mmol, dichloromethane). The mixture was stirred at room temperature overnight. The solvent and excess reagent were removed *in vacuo*. The residue was treated with 3-cyano-5-dimethylaminophenyl-amidoxime (40.8 mg, 0.2 mmol) and triethylamine (162 mg, 1.6 mmol) in dichloromethane (2 mL). The mixture was then heated in dimethylformamide (1 mL) for 4 hours at 130 °C. Standard work up, afforded 3.8 mg (5.8%) of 5-(5-chloro-pyrid-2-yl)-3-(3-cyano-5-dimethyaminophenyl)-1,2,4-

oxadiazole. ^{1}H-NMR ($CDCl_3$), δ (ppm): 8.82 (d, 1H), 8.27 (d, 1H), 7.95 (dd, 1H), 7.78 (s, 1H), 7.66 (d, 1H), 7.01 (d,1H), 3.06 (s, 6H).

5-(5-Chloro-pyrid-2-yl)-3-(3-cyano-5-methoxyphenyl)-1,2,4-oxadiazole

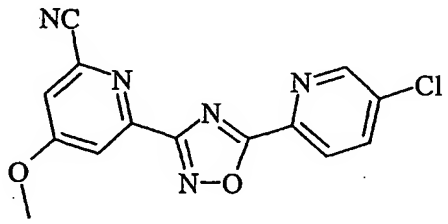
B197



A mixture of 5-chloropicolinic acid hydrochloride (72 mg, 0.4 mmol) in dichloromethane (2 mL) was treated with 2M oxalyl chloride (0.8 ml, 1.6 mmol, dichloromethane). The mixture was stirred at room temperature overnight. The solvent and excess reagent were removed *in vacuo*. The residue was treated with 3-cyano-5-methoxyphenyl-amidoxime (76 mg, 0.4 mmol) and triethylamine (162 mg, 1.6 mmol) in dichloromethane (2 mL). The mixture was then heated in dimethylformamide (1 mL) for 4 hours at 130 °C. Standard work up, afforded 45.8 mg (36.6%) of 5-(5-chloro-pyrid-2-yl)-3-(3-cyano-5-methoxyphenyl)-1,2,4-oxadiazole. ^{1}H-NMR ($CDCl_3$), δ (ppm): 8.85 (d, 1H), 8.27 (d, 1H), 8.10 (s, 1H), 7.95 (m, 2H), 7.12 (d, 1H), 3.92 (s, 3H).

5-(5-Chloro-pyrid-2-yl)-3-(6-cyano-4-methoxy-pyrid-2-yl)-1,2,4-oxadiazole

B198

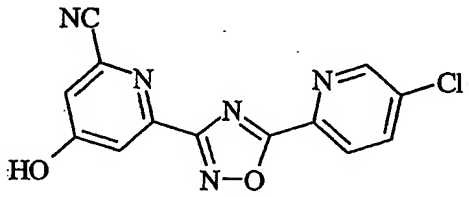


A mixture of 5-chloropicolinic acid hydrochloride (72 mg, 0.4 mmol) in dichloromethane (2 mL) was treated with 2M oxalyl chloride (0.8 ml, 1.6 mmol, dichloromethane). The mixture was stirred at room temperature overnight. The

solvent and excess reagent were removed *in vacuo*. The residue was treated with 6-cyano-4-methoxypyrid-2-yl-amidoxime (38.4 mg, 0.2 mmol) and triethylamine (162 mg, 1.6 mmol) in dichloromethane (2 mL). The mixture was then heated in dimethylformamide (1 mL) for 4 hours at 130 °C. Standard work up, afforded 1.9 mg (3%) of 5-(5-chloro-pyrid-2-yl)-3-(6-cyano-4-methoxypyrid-2-yl)-1,2,4-oxadiazole. [^{1}H-NMR ($CDCl_3$), δ (ppm): 8.85 (d, 1H), 8.36 (d, 1H), 7.97 (m, 2H), 7.38 (d, 1H), 4.03 (s, 3H)].

5-(5-chloro-pyrid-2-yl)-3-(6-cyano-4-hydroxy-pyrid-2-yl)-1,2,4-oxadiazole

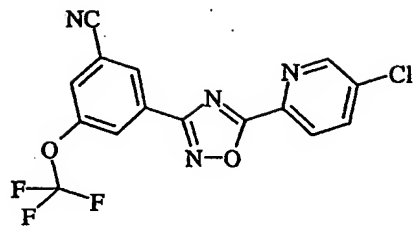
B199



A mixture of 5-chloropicolinic acid hydrochloride (72 mg, 0.4 mmol) in dichloromethane (2 mL) was treated with 2M oxalyl chloride (0.8 ml, 1.6 mmol, dichloromethane). The mixture was stirred at room temperature overnight. The solvent and excess reagent were removed *in vacuo*. The residue was treated with 6-cyano-4-methoxypyrid-2-yl-amidoxime (38.4 mg, 0.2 mmol) and triethylamine (162 mg, 1.6 mmol) in dichloromethane (2 mL). The mixture was then heated in dimethylformamide (1 mL) for 4 hours at 130 °C. Standard work up, afforded 2.2 mg (3.67%) of 5-(5-chloro-pyrid-2-yl)-3-(6-cyano-4-hydroxypyrid-2-yl)-1,2,4-oxadiazole [^{1}H-NMR ($CDCl_3$), δ (ppm): 8.87 (d, 1H), 8.43 (d, 1H), 8.23 (dd, 1H), 7.91 (d, 1H), 7.57 (d, 1H).].

5-(5-Chloro-pyrid-2-yl)-3-(3-cyano-5-trifluoromethoxyphenyl)-1,2,4-oxadiazole

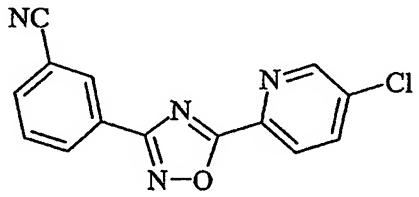
B200



A mixture of 5-chloropicolinic acid hydrochloride (72 mg, 0.4 mmol) in dichloromethane (2 mL) was treated with 2M oxalyl chloride (0.8 ml, 1.6 mmol, dichloromethane). The mixture was stirred at room temperature overnight. The solvent and excess reagent were removed *in vacuo*. The residue was treated with 3-cyano-5- trifluoromethoxyphenyl-amidoxime (68.6 mg, 0.28 mmol) and triethylamine (162 mg, 1.6 mmol) in dichloromethane (2 mL). The mixture was then heated in dimethylformamide (1 mL) for 4 hours at 130 °C. Standard work up, afforded 17.4 mg (16.9%) of 5-(5-chloro-pyrid-2-yl)-3-(3-cyano-5-trifluoromethoxyphenyl)-1,2,4-oxadiazole. ^{1}H-NMR ($CDCl_3$), δ (ppm): 8.84 (d, 1H), 8.46 (s, 1H), 8.30 (m, 2H), 7.96 (dd, 1H), 7.68 (d, 1H).

5-(5-Chloro-pyrid-2-yl)-3-(3-cyanophenyl)-1,2,4-oxadiazole

B201

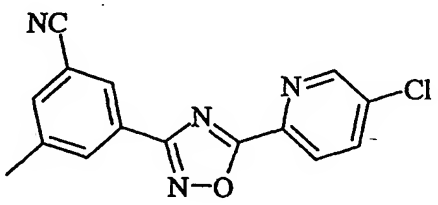


A mixture of 5-chloropicolinic acid hydrochloride (72 mg, 0.4 mmol) in dichloromethane (2 mL) was treated with 2M oxalyl chloride (0.8 ml, 1.6 mmol, dichloromethane). The mixture was stirred at room temperature overnight. The solvent and excess reagent were removed *in vacuo*. The residue was treated with 3-cyanophenyl-amidoxime (64.4 mg, 0.4 mmol) and triethylamine (162 mg, 1.6 mmol) in dichloromethane (2 mL). The mixture was then heated in dimethylformamide (1 mL) for 4 hours at 130 °C. Standard work up, afforded 24.5 mg (21.7%) of 5-(5-chloro-pyrid-2-yl)-3-(3-cyanophenyl)-1,2,4-oxadiazole. ^{1}H-NMR

($CDCl_3$), δ (ppm): 8.84 (d, 1H), 8.53 (s, 1H), 8.45 (dd, 1H), 8.26 (d, 1H), 7.95 (dd, 1H), 7.83 (d, 1H), 7.66 (t, 1H).

5-(5-Chloro-pyrid-2-yl)-3-(3-cyano-5-methylphenyl)-1,2,4-oxadiazole

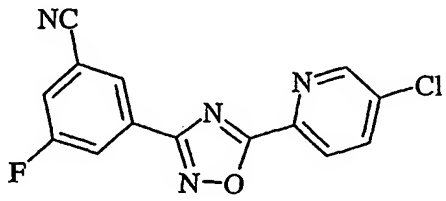
B202



A mixture of 5-chloropicolinic acid hydrochloride (72 mg, 0.4 mmol) in dichloromethane (2 mL) was treated with 2M oxalyl chloride (0.8 ml, 1.6 mmol, dichloromethane). The mixture was stirred at room temperature overnight. The solvent and excess reagent were removed *in vacuo*. The residue was treated with 3-cyano-5-methylphenyl-amidoxime (24 mg, 0.137 mmol) and triethylamine (162 mg, 1.6 mmol) in dichloromethane (2 mL). The mixture was then heated in dimethylformamide (1 mL) for 4 hours at 130 °C. Standard work up, afforded 21.2 mg (52%) of 5-(5-chloro-pyrid-2-yl)-3-(3-cyano-5-methylphenyl)-1,2,4-oxadiazole. ^{1}H-NMR ($CDCl_3$), δ (ppm): 8.84 (d, 1H), 8.28 (m, 3H), 7.9d (dd, 1H), 7.62 (s, 1H), 2.48 (s, 3H).

5-(5-Chloro-pyrid-2-yl)-3-(3-cyano-5-fluorophenyl)-1,2,4-oxadiazole

B203

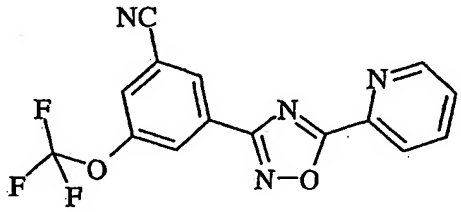


A mixture of 5-chloropicolinic acid hydrochloride (72 mg, 0.4 mmol) in dichloromethane (2 mL) was treated with 2M oxalyl chloride (0.8 ml, 1.6 mmol, dichloromethane). The mixture was stirred at room temperature overnight. The solvent and excess reagent were removed *in vacuo*. The residue was treated with 3-cyano-5-fluorophenyl-amidoxime (71.6 mg, 0.4 mmol) and triethylamine (162

mg, 1.6 mmol) in dichloromethane (2 mL). The mixture was then heated in dimethylformamide (1 mL) for 4 hours at 130 °C. Standard work up, afforded 70.4 mg (58.5%) of 5-(5-chloro-pyrid-2-yl)-3-(3-cyano-5-fluorophenyl)-1,2,4-oxadiazole. ^{1}H-NMR ($CDCl_3$), δ (ppm): 8.82 (d, 1H), 8.34 (d, 1H), 8.27 (d, 1H), 8.16 (dd, 1H), 7.97 (dd, 1H), 7.52 (dd, 1H).

3-(3-Cyano-5-trifluoromethoxyphenyl)-5-(2-pyridyl)-1,2,4-oxadiazole

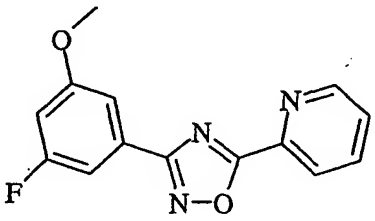
B204



A mixture of picolinic acid (123 mg, 1 mmol) and triethylamine (404 mg, 4 mmol) in tetrahydrofuran (2 mL) was treated with isobutylchloroformate (0.118 ml, 1.1 mmol) at room temperature. The mixture was stirred for 1.5 hours and treated with 3-cyano-5-trifluoromethoxyphenyl-amidoxime (50 mg, 0.204 mmol). The mixture was then heated in dimethylformamide (1 mL) for 4 hours at 130 °C. Standard work up, afforded 7.1 mg (10.5%) 3-(3-cyano-5-trifluoromethoxyphenyl)-5-(2-pyridyl)-1,2,4-oxadiazole. ^{1}H-NMR ($CDCl_3$), δ (ppm): 8.90 (d, 1H), 8.50 (s, 1H), 8.34 (m, 2H), 8.00 (dt, 1H), 7.66 (s, 1H), 7.60 (dd, 1H).

3-(3-Fluoro-5-methoxyphenyl)-5-(2-pyridyl)-1,2,4-oxadiazole

B205

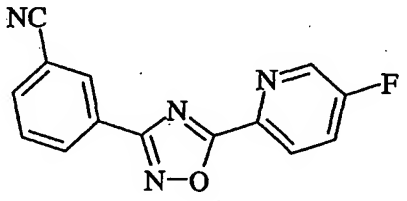


A mixture of picolinic acid (123 mg, 1 mmol) and triethylamine (404 mg, 4 mmol) in tetrahydrofuran (2 mL) was treated with isobutylchloroformate (0.118 ml,

1.1 mmol) at room temperature. The mixture was stirred for 1.5 hours and treated with 3-fluoro-5-methoxyphenyl-amidoxime (73.8 mg, 0.4 mmol). The mixture was then heated in dimethylformamide (1 mL) for 4 hours at 130 °C. Standard work up, afforded 40.1 mg (37%) 3-(3-fluoro-5-methoxyphenyl)-5-(2-pyridyl)-1,2,4-oxadiazole. ^{1}H-NMR ($CDCl_3$), δ (ppm): 8.90 (d, 1H), 8.30 (d, 1H), 7.95 (dt, 1H), 7.56 (m, 3H), 6.80 (dd, 1H), 3.73 (s, 3H).

3-(3-Cyanophenyl)-5-(5-fluoro-pyrid-2-yl)-1,2,4-oxadiazole

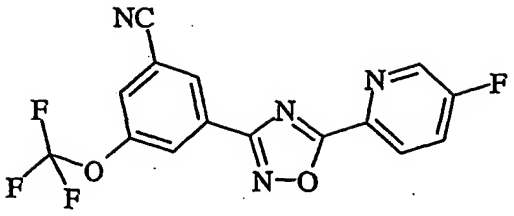
B206



A mixture of 5-fluoropicolinic acid hydrochloride (45.8 mg, 0.3 mmol) in dichloromethane (1 mL) was treated with 2M oxalyl chloride (0.6 ml, 1.2 mmol, dichloromethane). The mixture was stirred at room temperature for 3 hours. The solvent and excess reagent were removed *in vacuo*. The residue was treated with 3-cyanophenyl-amidoxime (24.2 mg, 0.15 mmol) and triethylamine (121mg, 1.2 mmol) in dichloromethane (1 mL). The mixture was then heated in dimethylformamide (1 mL) for 6 hours at 130 °C. Standard work up, afforded 10.6 mg (26.5%) of 3-(3-cyanophenyl)-5-(5-fluoro-pyrid-2-yl)-1,2,4-oxadiazole. ^{1}H-NMR ($CDCl_3$), δ (ppm): 8.72 (d, 1H), 8.53 (s, 1H), 8.45 (dd, 1H), 8.37 (dd, 1H), 7.83 (d, 1H), 7.68 (m, 2H).

3-(3-Cyano-5-trifluoromethoxyphenyl)-5-(5-fluoro-pyrid-2-yl)-1,2,4-oxadiazole

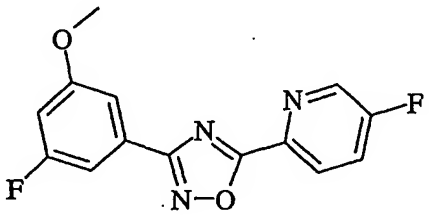
B207



A mixture of 5-fluoropicolinic acid hydrochloride (45.8 mg, 0.3 mmol) in dichloromethane (1 mL) was treated with 2M oxalyl chloride (0.6 ml, 1.2 mmol, dichloromethane). The mixture was stirred at room temperature for 3 hours. The solvent and excess reagent were removed *in vacuo*. The residue was treated with 3-cyano-5-trifluoromethoxyphenyl-amidoxime (36.5 mg, 0.15 mmol) and triethylamine (121mg, 1.2 mmol) in dichloromethane (1 mL). The mixture was then heated in dimethylformamide (1 mL) for 6 hours at 130 °C. Standard work up, afforded 7.2 mg (14.4%) of 3-(3-cyano-5-trifluoromethoxyphenyl)-5-(5-fluoro-pyrid-2-yl)-1,2,4-oxadiazole. ^{1}H-NMR ($CDCl_3$), δ (ppm): 8.74 (d, 1H), 8.49 (s, 1H), 8.38 (dd, 1H), 8.30 (s, 1H), 7.70 (m, 2H).

3-(3-Fluoro-5-methoxyphenyl)-5-(5-fluoropyrid-2-yl)-1,2,4-oxadiazole

B208

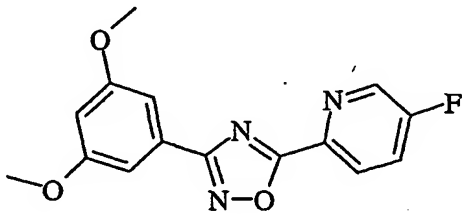


A mixture of 5-fluoropicolinic acid hydrochloride (45.8 mg, 0.3 mmol) in dichloromethane (1 mL) was treated with 2M oxalyl chloride (0.6 ml, 1.2 mmol, dichloromethane). The mixture was stirred at room temperature for 3 hours. The solvent and excess reagent were removed *in vacuo*. The residue was treated with 3-fluoro-5-methoxyphenyl-amidoxime (27.7 mg, 0.15 mmol) and triethylamine (121mg, 1.2 mmol) in dichloromethane (1 mL). The mixture was then heated in dimethylformamide (1 mL) for 6 hours at 130 °C. Standard work up, afforded 9.0 mg (20%) of 3-(3-fluoro-5-methoxyphenyl)-5-(5-fluoropyrid-2-yl)-1,2,4-oxadiazole.

^{1}H-NMR ($CDCl_3$), δ (ppm): 8.73 (d, 1H), 8.35 (dd, 1H), 7.65 (m, 1H), 7.55 (m, 2H), 6.80 (dd, 1H), 3.92 (s, 3H).

3-(3,5-Dimethoxyphenyl)-5-(5-fluoropyrid-2-yl)-1,2,4-oxadiazole

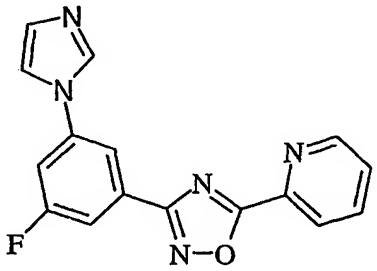
B209



A mixture of 5-fluoropicolinic acid hydrochloride (45.8 mg, 0.3 mmol) in dichloromethane (1 mL) was treated with 2M oxalyl chloride (0.6 ml, 1.2 mmol, dichloromethane). The mixture was stirred at room temperature for 3 hours. The solvent and excess reagent were removed *in vacuo*. The residue was treated with 3,5-dimethoxyphenyl-amidoxime (29.4 mg, 0.15 mmol) and triethylamine (121mg, 1.2 mmol) in dichloromethane (1 mL). The mixture was then heated in dimethylformamide (1 mL) for 6 hours at 130 °C. Standard work up, afforded 12 mg (26.6%) of 3-(3,5-dimethoxyphenyl)-5-(5-fluoropyrid-2-yl)-1,2,4-oxadiazole. ^{1}H-NMR ($CDCl_3$), δ (ppm): 8.71 (d, 1H), 8.37 (dd, 1H), 7.64 (dt, 1H), 7.37 (s, 2H), 6.61 (s, 1H), 3.87 (s, 6H).

3-[3-Fluoro-5-(1*H*-imidazol-1-yl)]phenyl]-5-(2-pyridyl)-1,2,4-oxadiazole

B210

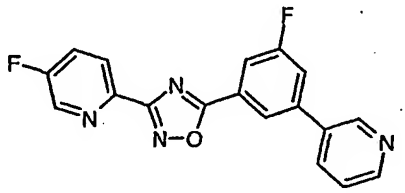


A mixture of picolinic acid (62 mg, 0.5 mmol) and triethylamine (202 mg, 2 mmol) in tetrahydrofuran (1 mL) was treated with isobutylchloroformate (0.059 ml, 0.55 mmol) at room temperature. The mixture was stirred for 2 hours and treated

with 3-fluoro-5-(1*H*-imidazol-1-yl)]phenyl-amidoxime (100 mg, 0.45 mmol). The mixture was then heated in dimethylformamide (1 mL) at 130 °C overnight. Standard work up, afforded 24.4 mg (17.6%) 3-[3-fluoro-5-(1*H*-imidazol-1-yl)]phenyl]-5-(2-pyridyl)-1,2,4-oxadiazole. ^{1}H-NMR ($CDCl_3$), δ (ppm): 8.90 (d, 1H), 8.32 (d, 1H), 8.10 (s, 1H), 7.7.98 (m, 3H), 7.58 (dd, 1H), 7.39 (s, 1H), 7.29 (m, 2H).

3-(5-Fluoro-2-pyridyl)-5-(3-fluoro-5-(3-pyridyl)phenyl)-1,2,4-oxadiazole

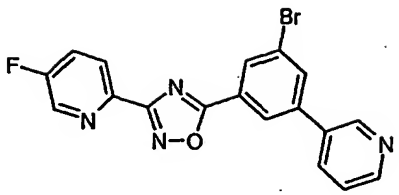
B211



A mixture of the hydrochloride salt of 3-Fluoro-5-(3-pyridyl)benzoic acid (1.00 g, 3.93 mmol) in dichloromethane (10 ml) was treated with oxalyl chloride (5.9 ml, 11.8 mmol, 2M dichloromethane) and 3 drops of *N,N*-dimethylformamide. The mixture was stirred 4 hours at room temperature. The solvent and excess reagent were removed *in-vacuo*. The residue was treated with 5-Fluoro-2-pyridylamidoxime (0.61 g, 3.93 mmol) and triethylamine (1.64 ml, 11.8 mmol) in dichloromethane (10 mL). The mixture was then heated in dimethylformamide (10 mL) at 120°C, overnight. Standard work up followed by trituration with diethyl ether afforded 3-(5-Fluoro-2-pyridyl)-5-(3-fluoro-5-(3-pyridyl)phenyl)-1,2,4-oxadiazole (452 mg) as a light yellow solid.

3-(5-Fluoro-2-pyridyl)-5-(3-bromo-5-(3-pyridyl)phenyl)-1,2,4-oxadiazole

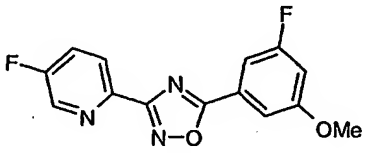
B212



A mixture of the hydrochloride salt of 3-Bromo-5-(3-pyridyl)benzoic acid (1.50 g, 4.78 mmol) in dichloromethane (10 ml) was treated with oxalyl chloride (7.2 ml, 14.3 mmol, 2M dichloromethane) and 3 drops of *N,N*-dimethylformamide. The mixture was stirred 4 hours at room temperature. The solvent and excess reagent were removed *in-vacuo*. The residue was treated with 5-Fluoro-2-pyridylamidoxime (0.74 g, 4.78 mmol) and triethylamine (2.0 ml, 14.3 mmol) in dichloromethane (10 mL). The mixture was then heated in dimethylformamide (10 mL) at 120°C, overnight. Standard work up followed by trituration with diethyl ether afforded 3-(5-Fluoro-2-pyridyl)-5-(3-bromo-5-(3-pyridyl)phenyl)-1,2,4-oxadiazole (457 mg) as an off white solid. ^{1}H-NMR ($CDCl_3$), δ (ppm): 8.91 (s, 1H), 8.70 (s, 2H), 8.42 (d, 2H), 8.27 (dd, 1H), 7.94 (m, 2H), 7.61 (dt, 1H), 7.44 (dd, 1H).

3-(5-Fluoro-2-pyridyl)-5-(3-fluoro-5-methoxyphenyl)-1,2,4-oxadiazole

B213

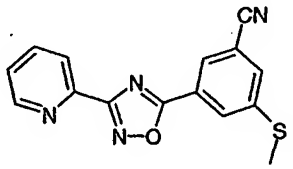


A mixture of 3-Fluoro-5-methoxybenzoic acid (0.20 g, 1.18 mmol) in dichloromethane (2.5 mL) was treated with oxalyl chloride (1.76 ml, 3.53 mmol, 2M dichloromethane) and 3 drops of *N,N*-dimethylformamide. The mixture was stirred 4 hours at room temperature. The solvent and excess reagent were removed *in-vacuo*. The residue was treated with 5-Fluoro-2-pyridylamidoxime (182 mg, 1.18 mmol) and triethylamine (0.49 ml, 3.53 mmol) in dichloromethane (2.5 mL). The mixture was then heated in dimethylformamide (2.5 mL) at 120°C, overnight.

Standard work up followed by purification on silica gel using 20% ethyl acetate in hexanes afforded the title compound (43.1 mg, 13%) as a light yellow solid. ^{1}H-NMR ($CDCl_3$), δ (ppm): 8.69 (d, 1H), 8.26 (dd, 2H), 7.60 (m, 3H), 6.87 (m, 1H).

3-(Pyrid-2-yl)-5-(3-cyano-5-thiomethylphenyl)-1,2,4-oxadiazole

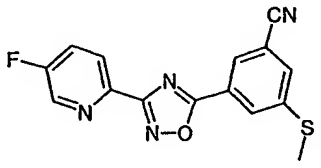
B214



Using the general procedure for the preparation of acid chlorides, 3-cyano-5-thiomethylbenzoyl chloride was prepared from 3-cyano-5-thiomethylbenzoic acid (330 mg, 1.71 mmol). A suspension of pyrid-2-ylamidoxime (123 mg, 0.9 mmol) in dichloromethane (4 mL) was treated with 3-cyano-5-thiomethylbenzoyl chloride (190 mg, 0.9 mmol) and the mixture stirred 30 minutes. The solvent was removed *in vacuo* and the intermediate dissolved in *N,N*-dimethylformamide (8 mL). The reaction was heated, under an argon atmosphere, for 20 hours at 120 °C. The reaction mixture was cooled and the solvent removed *in vacuo*. Silica gel chromatography using a gradient of 0% to 10% ethyl acetate in dichloromethane afforded 159 mg (60%) of 3-(pyrid-2-yl)-5-(3-cyano-5-thiomethylphenyl)-1,2,4-oxadiazole as a white solid: ^{1}H-NMR ($CDCl_3$), δ (ppm): 8.82 (t, 1H), 8.31 (d, 2H), 8.24 (d, 1H), 7.91 (t, 1H), 7.66 (s, 1H), 7.49 (t, 1H), 2.61 (s, 3H).

3-(5-Fluoro-pyrid-2-yl)-5-(3-cyano-5-thiomethylphenyl)-1,2,4-oxadiazole

B215

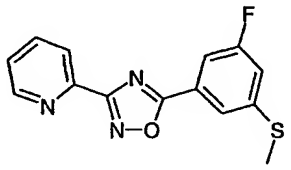


Using the general procedure for the preparation of acid chlorides, 3-cyano-5-thiomethylbenzoyl chloride was prepared from 3-cyano-5-thiomethylbenzoic acid (330 mg, 1.71 mmol). A suspension of 5-fluoro-pyrid-2-ylamidoxime (161 mg,

1.04 mmol) in dichloromethane (4 mL) was treated with 3-cyano-5-thiomethylbenzoyl chloride (220 mg, 1.04 mmol) and the mixture stirred 30 minutes. The solvent was removed *in vacuo* and the intermediate dissolved in *N,N*-dimethylformamide (8 mL). The reaction was heated, under an argon atmosphere, for 20 hours at 120 °C. After this time, the reaction mixture was cooled and the solvent removed *in vacuo*. Silica gel chromatography using a gradient of 5% to 50% ethyl acetate in hexanes afforded product that was not yet pure. The product was recrystallized from hexanes and methanol to yield 78 mg (24%) of 3-(5-fluoro-pyrid-2-yl)-5-(3-cyano-5-thiomethylphenyl)-1,2,4-oxadiazole as white solid: ^{1}H-NMR ($CDCl_3$), δ (ppm): 8.70 (s, 1H), 8.27 (t, 3H), 7.62 (m, 2H), 2.61 (s, 3H).

3-(Pyrid-2-yl)-5-(3-fluoro-5-thiomethylphenyl)-1,2,4-oxadiazole

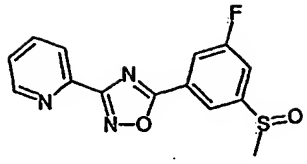
B216



Using the general procedure for the preparation of acid chlorides, 5-fluoro-3-thiomethylbenzoyl chloride was prepared from 5-fluoro-3-thiomethylbenzoic acid (470 mg, 2.52 mmol). A suspension of pyrid-2-ylamidoxime (346 mg, 2.52 mmol) in dichloromethane (3 mL) was treated with 5-fluoro-3-thiomethylbenzoyl chloride and the mixture was stirred 3 hours. The solvent was removed *in vacuo* and the intermediate dissolved in *N,N*-dimethylformamide (10 mL). The reaction was heated, under an argon atmosphere, for 4 hours at 120 °C. After this time, the reaction mixture was cooled and the solvent removed *in vacuo*. Silica gel chromatography using a gradient of 0% to 4% ethyl acetate in dichloromethane afforded 567 mg (78%) of 3-(pyrid-2-yl)-5-(5-fluoro-3-thiomethylphenyl)-1,2,4-oxadiazole as a white solid: ^{1}H-NMR ($CDCl_3$), δ (ppm): 8.85 (t, 1H), 8.21 (d, 1H), 7.89 (m, 2H), 7.72 (m, 1H), 7.47 (m, 1H), 7.15 (m, 1H), 2.57 (s, 3H).

3-(Pyrid-2-yl)-5-(3-fluoro-5-thiomethylsulphoxidephenyl)-1,2,4-oxadiazole

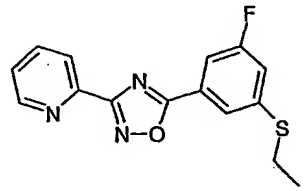
B217



3-(Pyrid-2-yl)-5-(3-fluoro-5-thiomethylphenyl)-1,2,4-oxadiazole (50 mg, 0.17 mmol) was dissolved in dichloromethane in an argon atmosphere at −78 °C and a solution of m-chloroperoxybenzoic acid (30 mg, 0.17 mmol) in dichloromethane was added. After 10 minutes, the reaction was allowed to warm to 0 °C and quenched with aqueous sodium bicarbonate. The reaction extracted with dichloromethane, washed with water and dried over anhydrous sodium sulphate. Column chromatography using 5% methanol in dichloromethane yielded 31 mg (59%) of 3-(Pyrid-2-yl)-5-(3-fluoro-5-thiomethylsulphoxidephenyl)-1,2,4-oxadiazole as an off-white solid. ^{1}H-NMR ($CDCl_3$), δ (ppm): 8.83 (d, 1H), 8.20 (t, 2H), 8.06 (m, 1H), 7.89 (m, 1H), 7.73 (m, 1H), 7.47 (m, 1H), 2.82 (s, 3H).

3-(Pyrid-2-yl)-5-(3-fluoro-5-thioethylphenyl)-1,2,4-oxadiazole

B218

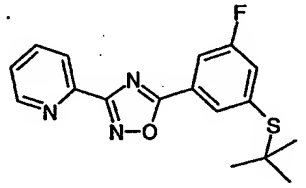


Using the general procedure for the preparation of acid chlorides, 5-fluoro-3-thioethylbenzoyl chloride was prepared from 5-fluoro-3-thioethylbenzoic acid (274 mg, 1.37 mmol). A suspension of pyrid-2-ylamidoxime (188 mg, 1.37 mmol) in dichloromethane (3 mL) was treated with 5-fluoro-3-thioethylbenzoyl chloride and the mixture was stirred 3 hours. The solvent was removed *in vacuo* and the intermediate dissolved in *N,N*-dimethylformamide (5 mL). The reaction was heated, under an argon atmosphere, for 12 hours at 120 °C. After this time, the reaction mixture was cooled and the solvent removed *in vacuo*. Silica gel chromatography using a gradient of 0% to 4% ethyl acetate in dichloromethane afforded 245 mg

(59%) of 3-(pyrid-2-yl)-5-(5-fluoro-3-thioethylphenyl)-1,2,4-oxadiazole as a white solid: ^{1}H-NMR ($CDCl_3$), δ (ppm): 8.76 (t, 1H), 8.12 (d, 1H), 7.83 (t, 1H), 7.77 (m, 1H), 7.65 (m, 1H), 7.39 (m, 1H), 7.12 (m, 1H), 2.96 (q, 2H), 1.28 (t, 3H).

3-(Pyrid-2-yl)-5-(3-fluoro-5-thioethylphenyl)-1,2,4-oxadiazole

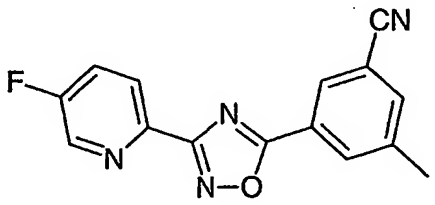
B219



Using the general procedure for the preparation of acid chlorides, 5-fluoro-3-thioethylbenzoyl chloride was prepared from 5-fluoro-3-thioethylbenzoic acid (274 mg, 1.20 mmol). A suspension of pyrid-2-ylamidoxime (165 mg, 1.20 mmol) in dichloromethane (3 mL) was treated with 5-fluoro-3-thiotertbutylbenzoyl chloride and the mixture was stirred 3 hours. The solvent was removed *in vacuo* and the intermediate dissolved in *N,N*-dimethylformamide (6 mL). The reaction was heated, under an argon atmosphere, for 12 hours at 120 °C. After this time, the reaction mixture was cooled and the solvent removed *in vacuo*. Silica gel chromatography using dichloromethane afforded 31 mg (8%) of 3-(pyrid-2-yl)-5-(5-fluoro-3-thiotertbutylphenyl)-1,2,4-oxadiazole as a white solid: ^{1}H-NMR ($CDCl_3$), δ (ppm): 8.85 (t, 1H), 8.24 (d, 1H), 7.97 (m, 1H), 7.89 (m, 1H), 7.48 (m, 1H), 1.34 (t, 9H).

(a) 3-(5-Fluoropyrid-2-yl)-5-(3-cyano-5-methylphenyl)-1,2,4-oxadiazole

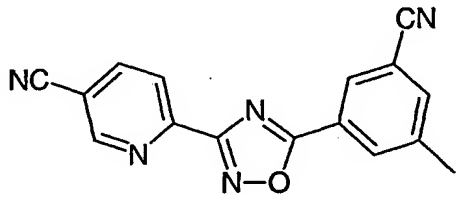
B220



To a mixture of 3-cyano-5-methylbenzoic acid (80 mg, 0.5 mmol), oxalyl chloride (1 mls, 2M solution in CH_2Cl_2, 2 mmol) in CH_2Cl_2 (5 ml) was added a few drops of DMF (one pipette drops) and the mixture was stirred at room temperature for 3 h. The solvent was then removed in vacuo. The residue was then dissolved in CH_2Cl_2 (5 ml) followed by the addition of 5-Fluoro-2-pyridyl amidoxime (78 mg, 0.5 mmol) and Et3N (0.2 ml) and stirring was continued for a further 1 h. Removal of the solvent in vacuo gave the crude residue which was dissolved in DMF (5 ml). The resulting solution was heated to 120°C overnight after which the solvent was removed in vacuo and the residue was trituated with 20% ethylacetate/hexane giving the product as a white solid (21 mg, 15% yield). 1HNMR(CDCl3) □: 8.70 (d, 1H), 8.37 (s,1H), 8.34 (s,1H), 8.28 (dd, 1H), 7.70 (s, 1H), 7.60 (dt, 1H), 2.50 (s, 3H).

(b) 3-(5-cyanopyrid-2-yl)-5-(3-cyano-5-methylphenyl)-1,2,4-oxadiazole

B221

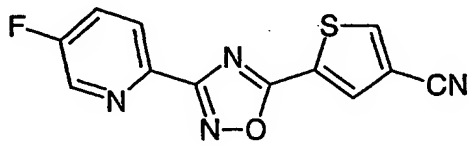


To a mixture of 3-cyano-5-methylbenzoic acid (81 mg, 0.5 mmol), oxalyl chloride (1 mls, 2M solution in CH_2Cl_2, 2 mmol) in CH_2Cl_2 (5 ml) was added a few drops of DMF (one pipette drops) and the mixture was stirred at room temperature for 3 h. The solvent was then removed in vacuo. The residue was then dissolved in CH_2Cl_2 (5 ml) followed by the addition of 5-cyano-2-pyridyl amidoxime (78 mg, 0.5 mmol) and Et3N (0.2 ml) and stirring was continued for a further 1 h. Removal of the solvent in vacuo gave the crude residue which was dissolved in DMF (5 ml). The resulting solution was heated to 120°C overnight after which the solvent was removed in vacuo and the residue was trituated with 20% ethylacetate/hexane giving the product as an off- white solid (10 mg, 7% yield). 1HNMR(CDCl3) □: 9.10

(d, 1H), 8.39 (d,1H), 8.37 (s,1H), 8.34 (s, 1H), 8.20 (dd, 1H), 7.75 (s, 1H), 2.60 (s, 3H).

(c) 3-(5-Fluoropyrid-2-yl)-5-(4-cyano-2-thienyl)-1,2,4-oxadiazole

B222

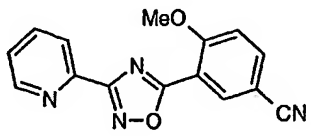


To a mixture of 4-cyano-2-thiophenecarboxylic acid (70 mg, 0.46 mmol), oxalyl chloride (1 mls, 2M solution in CH_2Cl_2, 2 mmol) in CH_2Cl_2 (5 ml) was added a few drops of DMF (one pipette drops) and the mixture was stirred at room temperature for 3 h. The solvent was then removed in vacuo. The residue was then dissolved in CH_2Cl_2 (5 ml) followed by the addition of 5-cyano-2-pyridyl amidoxime (71 mg, 0.46 mmol) and Et3N (0.2 ml) and stirring was continued for a further 1 h. Removal of the solvent in vacuo gave the crude residue which was dissolved in DMF (2 ml). The resulting solution was heated to 120°C overnight after which the solvent was removed in vacuo and the residue was trituated with 20% ethylacetate/hexane giving the product as an off- white solid (20 mg, 16% yield). 1HNMR(CDCl3) □: 8.68 (d, 1H), 8.25 (d,1H), 8.22 (s,1H), 8.17 (s, 1H), 7.61 (s, 1H).

EXAMPLE 6

3-(2-Pyridyl)-5-(5-cyano-2-methoxyphenyl)-1,2,4-oxadiazole

B97

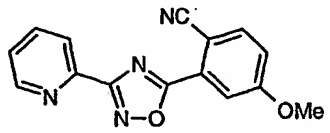


A mixture of 3-(2-pyridyl)-5-(5-bromo-2-methoxyphenyl)-1,2,4-oxadiazole (66.4 mg, 0.2 mmol), zinc cyanide (35.1 mg, 0.3 mmol), and

tetrakis(triphenylphosphine)palladium ($Pd(PPh_3)_4$, 23.1 mg, 0.02 mmol) in *N,N*-dimethylformamide (2 mL) was heated under an argon atmosphere at 80 °C for 16 hours. After cooling, the reaction mixture was poured into water and the crude product extracted with dichloromethane. Silica gel chromatography using 30% ethyl acetate in hexane afforded 6.9 mg (12%) of 3-(2-pyridyl)-5-(5-cyano-2-methoxyphenyl)-1,2,4-oxadiazole.

3-(2-pyridyl)-5-(2-cyano-5-methoxyphenyl)-1,2,4-oxadiazole

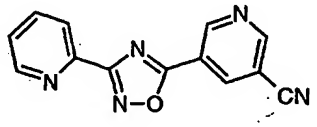
B98



In a similar fashion, a mixture of 3-(2-pyridyl)-5-(2-bromo-5-methoxyphenyl)-1,2,4-oxadiazole (33.2 mg, 0.1 mmol), zinc cyanide (17.6 mg, 0.15 mmol) and $Pd(PPh_3)_4$ (11.5 mg, 0.01 mmol) in *N,N*-dimethylformamide (1 mL) was heated under an argon atmosphere at 80 °C for 16 hours. After cooling, the reaction mixture was poured into water and the crude product extracted with dichloromethane. Silica gel chromatography using 50% ethyl acetate in hexane afforded 1.1 mg (4 %) of 3-(2-pyridyl)-5-(2-cyano-5-methoxyphenyl)-1,2,4-oxadiazole.

3-(2-Pyridyl)-5-(5-cyano-pyrid-3-yl)-1,2,4-oxadiazole

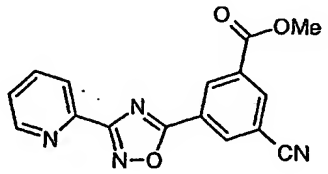
B99



In a similar fashion, mixture of 3-(2-pyridyl)-5-[3-(5-bromo-pyridyl)]-1,2,4-oxadiazole (90.9 mg, 0.3 mmol), zinc cyanide (24.6 mg, 0.21 mmol) and $Pd(PPh_3)_4$ (34.7 mg, 0.03 mmol) in *N,N*-dimethylformamide (1 mL) was stirred under an argon atmosphere at 80 °C for 16 hours. After cooling, the reaction mixture was poured into water and the crude product extracted with dichloromethane. Silica gel chromatography afforded 16 mg (21%) of 3-(2-pyridyl)-5-(5-cyano-pyrid-3-yl)-1,2,4-oxadiazole.

3-(2-Pyridyl)-5-(3-cyano-5-(methoxycarbonyl)phenyl)-1,2,4-oxadiazole

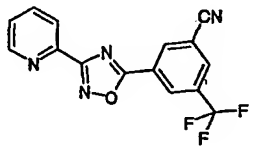
B100



In a similar fashion, a solution of 3-(2-pyridyl)-5-(3-iodo-5-(methoxycarbonyl)phenyl)-1,2,4-oxadiazole (50 mg, 0.122 mmol) in *N,N*-dimethylformamide (2 mL) was treated with zinc cyanide (22.5 mg, 0.191 mmol), and $Pd(PPh_3)_4$ (14 mg, 0.012 mmol). The reaction mixture was heated at 80 °C under an argon atmosphere for 2 hours. The mixture was then diluted with ethyl acetate (25 mL) and washed with water (3 x 5 mL) and brine (3 x 5 mL). The organic solution was then dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. Silica gel chromatography using 30% ethyl acetate in hexane afforded 29.2 mg (78%) of 3-(2-pyridyl)-5-(3-cyano-5-(methoxycarbonyl)phenyl)-1,2,4-oxadiazole: ^{1}H-NMR ($CDCl_3$), δ (ppm): 9.19 (s, 1H), 8.89 (d, 1H), 8.80 (s, 1H), 8.59 (s, 1H), 8.25 (d, 1H), 7.95 (t, 1H), 7.50 (m, 1H), 4.09 (s, 3H).

3-(2-Pyridyl)-5-(3-cyano-5-trifluoromethylphenyl)-1,2,4-oxadiazole

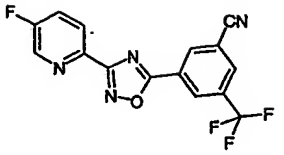
B223



Using the general procedure for the preparation of acid chlorides, 3-iodo-5-trifluoromethylbenzoyl chloride was prepared from 3-iodo-5-trifluoromethylbenzoic acid (711 mg, 4.46 mmol). To a solution of the acid chloride in dichloromethane (10 mL), pyridylamidoxime (217.7 mg, 1.588 mmol) was added. The solution was stirred at room temperature for 10 minutes and then concentrated *in vacuo*. DMF (8mL) was added to the residue and the resulting solution was stirred at 120°C for 16 h under argon. After the reaction mixture was cooled to room temperature, the solvent was removed *in vacuo*. Flash chromatography on silica gel (10%-20% ethyl acetate in hexane) yielded 439 mg (66%) of 3-(2-pyridyl)-5-(3-iodo-5-trifluoromethylphenyl)-1,2,4-oxadiazole. This intermediate (100.8 mg, 241.6 mmol), zinc cyanide (34.7 mg, 296 mmol) and tetrakistriphenyphosphine palladium(0) ($Pd(PPh_3)_4$, 30.5mg, 0.026mmol) were mixed and flushed with argon. DMF (1 mL) was added and the resulting solution was stirred for 2 h at 80 °C. After cooling to room temperature the reaction mixture was filtered through celite and washed with ethyl acetate (50 mL). The crude mixture was extracted into ethyl acetate (100 mL), washed sequentially with water (3X50mL) and brine (50mL), and dried over sodium sulfate. Flash chromatography on silica gel (50% ethyl acetate in hexane) yielded 53 mg (69%, GC/MS purity 97%) of 3-(2-pyridyl)-5-(3-cyano-5-trifluoromethylphenyl)-1,2,4-oxadiazole. ^{1}H-NMR ($CDCl_3$), δ (ppm): 8.87 (d, 1H), 8.80 (s, 1H), 8.78 (s, 1H), 8.24 (d, 1H), 8.15 (s, 1H), 7.92 (m, 1H), 7.51 (m, 1H).

3-(5-Fluoro-2-pyridyl)-5-(3-cyano-5-trifluoromethylphenyl)-1,2,4-oxadiazole

B224

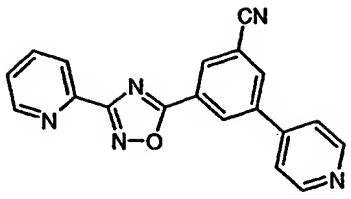


In a similar fashion, 3-iodo-5-trifluoromethylbenzoyl chloride was prepared from 3-iodo 5-trifluoromethylbenzoic acid (118. 2 mg, 0.374 mmol). To a solution of the acid chloride in dichloromethane (2 mL), 5-fluoropyridylamidoxime (124.4 mg, 0.3861 mmol) was added. The solution was stirred at room temperature for 10 minutes and then concentrated *in vacuo*. DMF (8mL) was added to the residue and the resulting solution was stirred at 120°C for 16 h under argon. After the reaction mixture was cooled to room temperature, the solvent was removed *in vacuo*. Flash chromatography on silica gel (10%-20% ethyl acetate in hexane) yielded 38.6 mg (24.4%) of 3-(5-fluoro-2-pyridyl)-5-(3-iodo-5-trifluoromethylphenyl)-1,2,4-oxadiazole. This intermediate (38.6 mg, 0.089 mmol), zinc cyanide (16.8 mg, 0.143 mmol) and $Pd(PPh_3)_4$ (11.8mg, 0.01 mmol) were mixed and flushed with argon. DMF (2 mL) was added and the resulting solution was stirred for 1 h at 80 °C. After cooling to room temperature the reaction mixture was filtered through celite and washed with ethyl acetate (50 mL). The crude mixture was extracted into ethyl acetate (300 mL), washed sequentially with water (6X50mL) and brine (50mL), and dried over sodium sulfate. Trituration of the solid with ether yielded 7.5 mg (26%) of 3-(5-fluoro-2-pyridyl)-5-(3-cyano-5-trifluoromethylphenyl)-1,2,4-oxadiazole. ^{1}H-NMR ($CDCl_3$), δ (ppm): 8.78 (s, 1H), 8.75 (s, 1H), 8.72 (s, 1H), 8.27 (m, 1H), 8.16 (s, 1H), 7.63 (m, 1H).

EXAMPLE 7

3-(2-Pyridyl)-5-(3-cyano-5-(4-pyridyl)phenyl)-1,2,4-oxadiazole

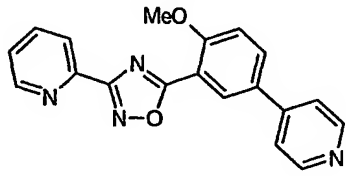
B101



A mixture of 3-(2-pyridyl)-5-(3-bromo-5-cyanophenyl)-1,2,4-oxadiazole (70 mg, 0.21 mmol), 4-pyridylboronic acid (53 mg, 0.43 mmol), and tetrakis(triphenylphosphine) palladium(0) ($Pd(PPh_3)_4$, 25 mg, 0.021 mmol) in a solution of ethylene glycol dimethyl ether (3mL) and 2M sodium carbonate (3 mL) was headed in a sealed vial at 100°C for 1 hour with vigorous stirring. The reaction was cooled and diluted with chloroform. The organic solution was washed with water and saturated brine, filtered, and concentrated. Silica gel chromatography of the residue using a gradient of 50% ethyl acetate in hexane to 100% ethyl acetate followed by trituration with 5% ethyl acetate in diethyl ether afforded 6 mg (9 %) of 3-(2-pyridyl)-5-(3-cyano-5-(4-pyridyl)phenyl)-1,2,4-oxadiazole: ^1H NMR ($CDCl_3$): δ - 8.88 (d, 1H), 8.78 (m, 3H), 8.64 (s, 1H), 8.26 (d, 1H), 8.15 (s, 1H), 7.93 (t, 1H), 7.61 (m, 2H), 7.52 (m, 1H).

3-(2-Pyridyl)-5-[2-methoxy-5-(4-pyridyl)phenyl]-1,2,4-oxadiazole

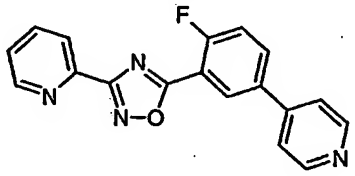
B102



In a similar fashion, 3-(2-pyridyl)-5-(5-bromo-2-methoxyphenyl)-1,2,4-oxadiazole (66.4 mg, 0.2 mmol), 4-pyridylboronic acid (48.8 mg, 0.4 mmol), and $Pd(PPh_3)_4$ (23 mg, 0.02 mmol) in a solution of 2M sodium carbonate (2 mL) and ethylene glycol dimethyl ether (2 mL) was heated overnight at 105 °C. Standard work up, afforded 6.6 mg (10%) of 3-(2-pyridyl)-5-[2-methoxy-5-(4-pyridyl)phenyl]-1,2,4-oxadiazole.

3-(2-Pyridyl)-5-[2-fluoro-5-(4-pyridyl)phenyl]-1,2,4-oxadiazole

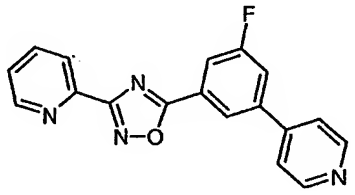
B103



In a similar fashion, 3-(2-pyridyl)-5-(5-bromo-2-fluorophenyl)-1,2,4-oxadiazole (100 mg, 0.312 mmole), 4-pyridylboronic acid (76.7 mg,0.6265 mmol) and $Pd(PPh_3)_4$ (36.1 mg, 0.03123 mmol) in a solution of 2M sodium carbonate (4 mL) and ethylene glycol dimethyl ether (4 mL) was heated overnight at 105 °C. Standard work up, afforded 4.1 mg (4%) of 3-(2-pyridyl)-5-[2-fluoro-5-(4-pyridyl)phenyl]-1,2,4-oxadiazole.

3-(2-Pyridyl)-5-(3-fluoro-5-(4-pyridyl)phenyl)-1,2,4-oxadiazole

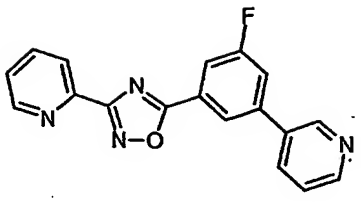
B104



In a similar fashion, 3-(2-pyridyl)-5-(3-bromo-5-fluorophenyl)-1,2,4-oxadiazole (30 mg, 0.093 mmol), pyridine-4-boronic acid (17.1 mg, 0.093 mmol), and $Pd(PPh_3)_4$ (10.4 mg, 0.0093 mmol) in a solution of and ethylene glycol dimethyl ether (1mL) and 2M sodium carbonate (1mL) was heated in a sealed vial at 100°C for 1 hour. Standard work up and silica gel chromatography using a gradient of 50% ethyl acetate in hexane to 100% ethyl acetate afforded 2 mg (7%) of 3-(2-pyridyl)-5-(3-fluoro-5-(4-pyridyl)phenyl)-1,2,4-oxadiazole: ^{1}H-NMR ($CDCl_3$), δ (ppm): 8.88 (d, 1H), 8.79 (d, 2H), 8.40 (s, 1H), 8.25 (d, 1H), 8.06 (md, 1H), 7.90 (td, 1H), 7.60 (m, 3H), 7.50 (ddd, 1H).

3-(2-Pyridyl)-5-(3-fluoro-5-(3-pyridyl)phenyl)-1,2,4-oxadiazole

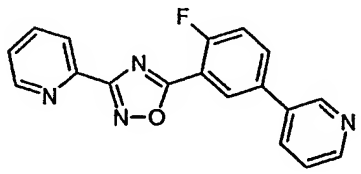
B105



A mixture of 3-(2-pyridyl)-5-(3-bromo-5-fluorophenyl)-1,2,4-oxadiazole (100 mg, 0.312 mmol), pyridine-3-boronic acid 1,3-propanediol cyclic ester (102 mg, 0.624 mmol), and tetrakis(triphenylphosphine)palladium(0) ($Pd(PPh_3)_4$, 35.8 mg, 0.031 mmol), in a solution of ethylene glycol dimethyl ether (3 mL) and 2M sodium carbonate (3 mL) was heated in a sealed vial at 100°C for 1 hour. The reaction was cooled, diluted with chloroform, washed with water and saturated brine, filtered, and concentrated. Silica gel chromatography using a gradient of 50% ethyl acetate in hexane to 100% ethyl acetate afforded 19 mg (19%) 3-(2-pyridyl)-5-(3-fluoro-5-(3-pyridyl)phenyl)-1,2,4-oxadiazole: ^{1}H-NMR ($CDCl_3$), δ (ppm): 8.92 (s, 1H), 8.84 (d, 1H), 8.70 (d, 1H), 8.39 (s, 1H), 8.25 (d, 1H), 8.00 (m, 2H), 7.90 (td, 1H), 7.65 (m, 1H), 7.55 (m, 2H).

3-(2-Pyridyl)-5-[2-fluoro-5-(3-pyridyl)phenyl]-1,2,4-oxadiazole

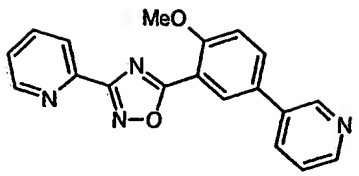
B106



In a similar fashion, 3-(2-pyridyl)-5-(5-bromo-2-fluorophenyl)-1,2,4-oxadiazole (100 mg, 0.312 mmol), pyridine-3-boronic acid 1,3-propanediol cyclic ester (101.8 mg, 0.625 mmol) and $Pd(PPh_3)_4$ (36.1 mg, 0.0312 mmole) in a solution of 2M sodium carbonate (4 mL) and ethylene glycol dimethyl ether (4 mL) was heated overnight at 105 °C. Standard work up afforded 8.7 mg (9%) 3-(2-pyridyl)-5-[2-fluoro-5-(3-pyridyl)phenyl]-1,2,4-oxadiazole.

3-(2-Pyridyl)-5-[2-methoxy-5-(3-pyridyl)phenyl]-1,2,4-oxadiazole

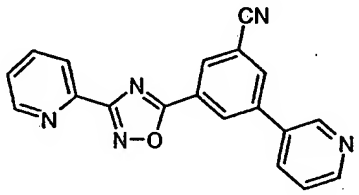
B107



In a similar fashion, 3-(2-pyridyl)-5-(5-bromo-2-methoxyphenyl)-1,2,4-oxadiazole (66.4 mg, 0.2 mmol), pyridine-3-boronic acid 1,3-propanediol cyclic ester (65 mg, 0.4 mmol), and $Pd(PPh_3)_4$ (23 mg, 0.02 mmol) in a solution of 2M sodium carbonate (2 mL) and ethylene glycol dimethyl ether (2 mL) was heated overnight at 105 °C. Standard work up afforded 21 mg (32%) 3-(2-pyridyl)-5-[2-methoxy-5-(3-pyridyl)phenyl]-1,2,4-oxadiazole.

3-(2-Pyridyl)-5-(3-cyano-5-(3-pyridyl)phenyl)-1,2,4-oxadiazole

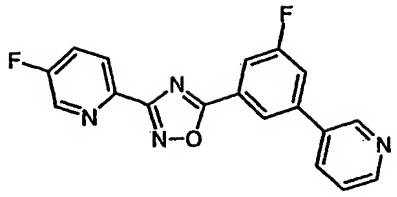
B108



In a similar fashion, 3-(2-pyridyl)-5-(3-bromo-5-cyanophenyl)-1,2,4-oxadiazole (71 mg, 0.22 mmol), pyridine-3-boronic acid 1,3-propanediol cyclic ester (70 mg, 0.43 mmol), and $Pd(PPh_3)_4$ (25 mg, 0.022 mmol) in a solution of ethylene glycol dimethyl ether (3 mL) and 2M sodium carbonate (3 mL) was heated in a sealed vial at 100°C for 1 hour. Standard work up and silica gel chromatography using a gradient of 50% ethyl acetate in hexane to 100% ethyl acetate followed by trituration with 5% ethyl acetate in diethyl ether afforded 16 mg (22 %) of 3-(2-pyridyl)-5-(3-cyano-5-(3-pyridyl)phenyl)-1,2,4-oxadiazole: ^1H NMR ($CDCl_3$): δ - 8.94 (d, 1H), 8.88 (d, 1H), 8.74 (m, 2H), 8.61 (s, 1H), 8.25 (d, 1H), 8.00 (s, 1H), 7.98 (m, 1H), 7.93 (m, 1H), 7.50 (m, 2H).

3-(5-Fluoro-2-pyridyl)-5-(3-fluoro-5-(3-pyridyl)phenyl)-1,2,4-oxadiazole

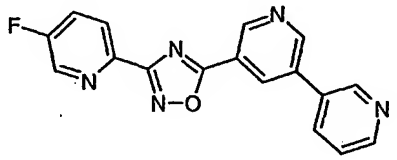
B109



In a similar fashion, 3-(5-fluoro-2-pyridyl)-5-(3-bromo-5-fluorophenyl)-1,2,4-oxadiazole (60 mg, 0.154 mmol), pyridine-3-boronic acid 1,3-propanediol cyclic ester (50.4 mg, 0.309 mmol), and $Pd(PPh_3)_4$ (17.8 mg, 0.015 mmol), in a solution of ethylene glycol dimethyl ether (2 mL) and 2M sodium carbonate (2 mL) was heated in a selaed vial at 100°C for 1 hour. Standard work up and silica gel chromatography using a gradient of 50% to 70% ethyl acetate in hexane afforded 24.7 mg (48%) of 3-(5-fluoro-2-pyridyl)-5-(3-fluoro-5-(3-pyridyl)phenyl)-1,2,4-oxadiazole: ^{1}H-NMR ($CDCl_3$), δ (ppm): 8.92 (d, 1H), 8.71 (m, 2H), 8.31 (s, 1H), 8.30 (dd, 1H), 8.00 (m, 2H), 7.62 (td, 1H), 7.57 (td, 1H), 7.45 (dd, 1H).

3-(5-Fluoropyrid-2-yl)-5-[5-(3-pyridyl)-pyrid-3-yl)]-1,2,4-oxadiazole

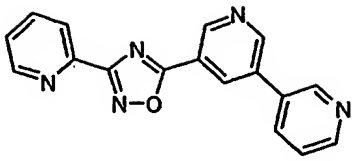
B110



In a similar fashion, 3-(5-fluoropyrid-2-yl)-5-(5-bromo-pyrid-3-yl)-1,2,4-oxadiazole (164 mg, 0.5 mmole), pyridine-3-boronic acid 1,3-propanediol cyclic ester (163.0 mg, 1 mmol) and $Pd(PPh_3)_4$ (57.8 mg, 0.05 mmol) in a solution of 2M sodium carbonate (2.5 mL) and ethylene glycol dimethyl ether (2.5 mL) was heated at 105 °C for 1 hour. Standard work up afforded 57 mg (18%) of 3-(5-fluoropyrid-2-yl)]-5-[5-(3-pyridyl)-pyrid-3-yl)]-1,2,4-oxadiazole.

3-(2-Pyridyl)-5-[5-(3-pyridyl)-pyrid-3-yl]-1,2,4-oxadiazole

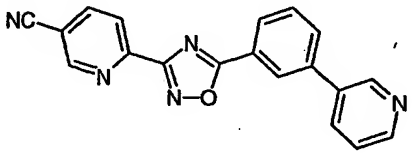
B111



In a similar fashion, 3-(2-pyridyl)-5-(5-bromo-pyrid-3-yl)-1,2,4-oxadiazole (60.6 mg, 0.2 mmole), pyridine-3-boronic acid 1,3-propanediol cyclic ester (48.9 mg, 0.3 mmol) and $Pd(PPh_3)_4$ (34.65 mg, 0.03 mmole) in a solution of 2M sodium carbonate (2 mL) and ethylene glycol dimethyl ether (2 mL) was heated overnight at 105 °C. Standard work up afforded 21 mg (35%) 3-(2-pyridyl)-5-[5-(3-pyridyl)-pyrid-3-yl]-1,2,4-oxadiazole.

3-(5-Cyanopyrid-2-yl)-5-(3-(pyrid-3-yl)phenyl)-1,2,4-oxadiazole

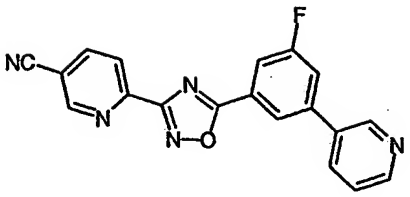
B112



In a similar fashion, 3-(5-cyanopyrid-2-yl)-5-(3-bromophenyl)-1,2,4-oxadiazole (50 mg, 0.15 mmol), pyridine-3-boronic acid 1,3-propanediol cyclic ester (50.5 mg, 0.31 mmol) and $Pd(PPh_3)_4$ (24 mg, 0.021 mmol) in a solution of ethylene glycol dimethyl ether (2 mL) and 2M sodium carbonate (2 mL) were heated in a sealed tube at 90 °C for 45 min. Standard work up, silica gel chromatography (gradient of 20% to 50% ethyl acetate in hexane) and trituration (diethyl ether) of the hydrochloride salt, afforded 11.7 mg (42%) of 3-(5-cyanopyrid-2-yl)-5-(3-(pyrid-3-yl)phenyl)-1,2,4-oxadiazole dihydrochloride: ^{1}H-NMR ($CDCl_3$), δ (ppm): 9.15 (s, 1H), 9.00 (s, 1H), 8.80 (s, 1H), 8.66 (d, 1H), 8.52 (s, 1H), 8.34 (m, 2H), 8.17 (dd, 1H), 8.02 (m, 1H), 7.95 (d, 1H) , 7.75 (t, 1H).

3-(5-Cyanopyrid-2-yl)-5-(3-fluoro-5-(pyrid-3-yl)phenyl)-1,2,4-oxadiazole

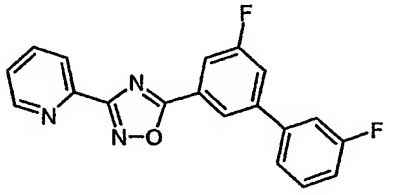
B113



In a similar fashion, 3-(5-cyanopyrid-2-yl)-5-(3-bromo-5-fluorophenyl)-1,2,4-oxadiazole (16.7 mg, 0.048 mmol), pyridine-3-boronic acid 1,3-propanediol cyclic ester (24 mg, 0.15 mmol) and $Pd(PPh_3)_4$ (12 mg, 0.01 mmol) in a solution of ethylene glycol dimethyl ether (1 mL) and 2M sodium carbonate (1 mL) were heated in a sealed tube at 90 °C for for 1 hour. Standard work up, silica gel chromatography (gradient of 20% to 50% ethyl acetate in hexane) and trituration (dichloromethane) of the hydrochloride salt, afforded 4.9 mg (24%) of 3-(5-cyanopyrid-2-yl)-5-(3-fluoro-5-(pyrid-3-yl)phenyl)-1,2,4-oxadiazole dihydrochloride (4.9 mg, 24%): ^{1}H-NMR ($CD_3OD/CDCl_3$), δ (ppm):□9.36 (s, 1H), 9.10 (s, 1H), 9.06 (d, 1H), 8.95 (d, 1H), 8.55 (s, 1H), 8.45 (m, 2H), 8.27 (t, 1H), 8.20 (d, 1H), 8.01 (d, 1H).

3-(2-Pyridyl)-5-[(3-(3-fluorophenyl)-5-fluorophenyl)]-1,2,4-oxadiazole

B114

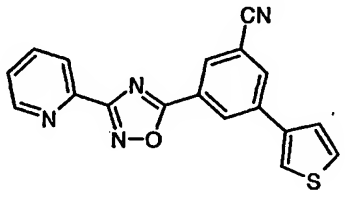


A mixture of 3-(2-pyridyl)-5-[(3-bromo-5-fluorophenyl)]-1,2,4-oxadiazole (55.5mg, 0.173mmol), 3-fluorophenyl boronic acid (48.4mg, 0.346mmol), tetrakis(triphenylphosphine)palladium(0) ($Pd(PPh_3)_4$ (20mg, 0.017mmol) in a solution of dimethoxy ethane (1.5 mL) and 2M sodium carbonate (1.5mL) was heated in a sealed vial overnight at 100 °C. After cooling, the reaction mixture was treated with water and the product extracted with dichloromethane (3x). Silica gel chromatography of the crude product using 30% ethyl acetate in hexane afforded

21.2mg (37%) of 3-(2-pyridyl)-5-[3-(3-fluorophenyl)-5-fluorophenyl)]-1,2,4-oxadiazole: m.p. 146-150 °C.

3-(2-Pyridyl)-5-(3-cyano-5-(3-thiophene)phenyl)-1,2,4-oxadiazole

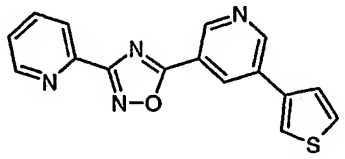
B115



In a similar fashion, 3-(2-pyridyl)-5-(3-bromo-5-cyanophenyl)-1,2,4-oxadiazole (70 mg, 0.21 mmol), 3-thiopheneboronic acid (55 mg, 0.43 mmol), $Pd(PPh_3)_4$ (25 mg, 0.021 mmol) in a solution of 2M sodium carbonate (3 mL) and ethylene glycol dimethyl ether (3 mL) was heated at 100°C for 1 hour. Standard work up and silica gel chromatography using a gradient of 10% to 30% ethyl acetate in hexane afforded 22 mg (31 %) of 3-(2-pyridyl)-5-(3-cyano-5-(3-thiophene)phenyl)-1,2,4-oxadiazole: ^1H NMR ($CDCl_3$): δ - 8.87 (d, 1H), 8.71 (s, 1H), 8.46 (s, 1H), 8.25 (d, 1H), 8.08 (s, 1H), 7.92 (t, 1H), 7.69 (s, 1H), 7.50 (m, 3H).

3-(2-Pyridyl)-5-[5-(3-thienyl)-pyrid-3-yl]-1,2,4-oxadiazole

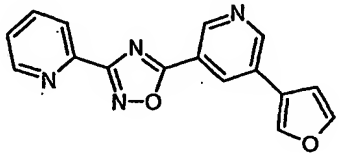
B116



In a similar fashion, 3-(2-pyridyl)-5-(5-bromo-pyrid-3-yl)-1,2,4-oxadiazole (42 mg, 0.1385 mmol), 3-thiopheneboronic acid (26.6 mg, 0.208 mmol), and $Pd(PPh_3)_4$ (24.0 mg, 0.021 mmole) in a solution of 2M sodium carbonate (1.5 mL) and ethylene glycol dimethyl ether (1.5 mL) was heated overnight at 105 °C. Standard work up afforded 3.2 mg (8%) of 3-(2-pyridyl)-5-[5-(3-thienyl)-pyrid-3-yl]-1,2,4-oxadiazole.

3-(2-Pyridyl)-5-[5-(3-furyl)-pyrid-3-yl]-1,2,4-oxadiazole

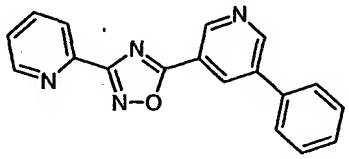
B117



In a similar fashion, 3-(2-pyridyl)-5-(5-bromo-pyrid-3-yl)-1,2,4-oxadiazole (152 mg, 0.5 mmol), 3-furylboronic acid (111.9 mg, 1.0 mmole) and $Pd(PPh_3)_4$ (57.8 mg, 0.05 mmole) in a solution of 2M sodium carbonate (3 mL) and ethylene glycol dimethyl ether (3 mL) was heated overnight at 105 °C. Standard work up afforded 47 mg (32%) of 3-(2-pyridyl)-5-[5-(3-furyl)-pyrid-3-yl]-1,2,4-oxadiazole.

3-(2-Pyridyl)-5-(5-phenyl-pyrid-3-yl)-1,2,4-oxadiazole

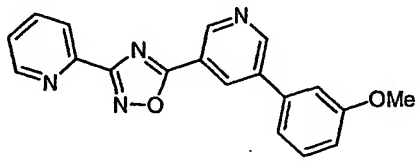
B118



In a similar fashion, 3-(2-pyridyl)-5-(5-bromo-pyrid-3-yl)-1,2,4-oxadiazole (152 mg, 0.5 mmol), phenylboronic acid (121.9 mg, 1.0 mmol) and $Pd(PPh_3)_4$ (57.8 mg, 0.05 mmol) in a solution of 2M sodium carbonate (3 mL) and ethylene glycol dimethyl ether (3 ml) was heated overnight at 105 °C. Standard work up afforded 45 mg of 3-(2-pyridyl)-5-(5-phenyl-pyrid-3-yl)-1,2,4-oxadiazole.

3-(2-Pyridyl)-5-[5-(3-methoxyphenyl)-pyrid-3-yl]-1,2,4-oxadiazole

B119

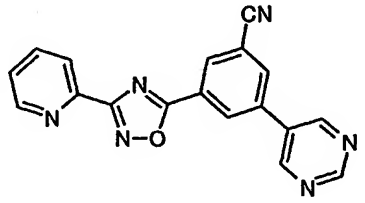


In a similar fashion, 3-(2-pyridyl)-5-[3-(5-bromo-pyridyl)]-1,2,4-oxadiazole (45 mg, 0.148 mmol), 3-methoxyphenylboronic acid (45mg, 0.296 mmol), and

$Pd(PPh_3)_4$ (25 mg, 0.022 mmol) in a solution of 2M sodium carbonate (1 mL) and ethylene glycol dimethoxy ether (1 mL) was heated at 105 °C for 2 hours. Standard work up afforded 14.8 mg of 3-(2-pyridyl)-5-[5-(3-methoxyphenyl)-pyrid-3-yl]-1,2,4-oxadiazole.

3-(2-Pyridyl)-5-(3-cyano-5-(5-pyrimidyl)phenyl)-1,2,4-oxadiazole

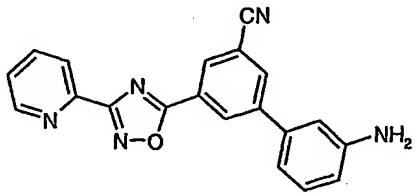
B120



In a similar fashion, 3-(2-pyridyl)-5-(3-bromo-5-cyanophenyl)-1,2,4-oxadiazole (71 mg, 0.22 mmol), pyrimidyl-5-boronic acid pinacolate (89 mg, 0.43 mmol), and $Pd(PPh_3)_4$ (25 mg, 0.022 mMol) in a solution of 2M sodium carbonate (3 mL) and ethylene glycol dimethyl ether (3 mL) was heated in a sealed vial at 100°C for 1 hour. Standard work up and silica gel chromatography using a gradient of 30% ethyl acetate in hexane to 100% ethyl acetate, followed by trituration with ethyl acetate afforded 4 mg (6 %) of 3-(2-pyridyl)-5-(3-cyano-5-(5-pyrimidyl)phenyl)-1,2,4-oxadiazole: ^1H NMR ($CDCl_3$): δ - 9.37 (s, 1H), 9.07 (s, 2H), 8.89 (d, 1H), 8.76 (s, 1H), 8.67 (s, 1H), 8.26 (d, 1H), 8.11 (s, 1H), 7.94 (t, 1H), 7.52 (m, 1H).

3-(2-Pyridyl)-5-(3-cyano-5-(3-aminophenyl)phenyl)-1,2,4-oxadiazole

B121

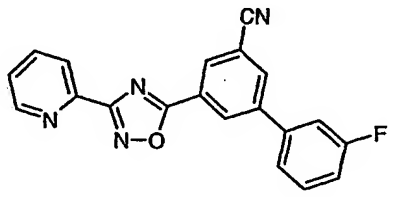


In a similar fashion, 3-(2-pyridyl)-5-(3-bromo-5-cyanophenyl)-1,2,4-oxadiazole (70 mg, 0.21 mmol), 3-aminophenylboronic acid (66 mg, 0.43 mmol),

and $Pd(PPh_3)_4$ (25 mg, 0.021 mmol), in a solution of ethylene glycol dimethyl ether (3 mL) and 2M sodium carbonate (3 mL) was heated in a sealed vial at 100°C for 1 hour. Standard work up and silica gel chromatography using a gradient of 30% ethyl acetate in hexane to 100% ethyl acetate, followed by trituration with 50% ethyl acetate in hexane afforded 32mg (45 %) of 3-(2-pyridyl)-5-(3-cyano-5-(3-aminophenyl)phenyl)-1,2,4-oxadiazole: ^1H NMR ($CDCl_3$): δ - 8.82 (d, 1H), 8.57 (s, 2H), 8.40 (s, 1H), 8.22 (d, 1H), 8.08 (t, 1H), 7.66 (m, 1H), 7.20 (t, 1H), 7.00 (m, 2H), 6.69 (d, 1H).

3-(2-Pyridyl)-5-(3-cyano-5-(3-fluorophenyl)phenyl)-1,2,4-oxadiazole

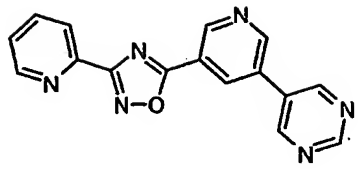
B122



In a similar fashion, 3-(2-pyridyl)-5-(3-bromo-5-cyanophenyl)-1,2,4-oxadiazole (70 mg, 0.21 mmol), 3-fluorophenylboronic acid (60 mg, 0.43 mmol), and $Pd(PPh_3)_4$ (25 mg, 0.022 mmol) in a solution of ethylene glycol dimethyl ether (3 mL) and 2M sodium carbonate (3 mL) was heated in a sealed vial at 100 °C for 1 hour. Standard work up and silica gel chromatography using a mixture of hexane:ethyl acetate:dichloromethane (3.5:0.5:4), followed by trituration with diethyl ether afforded 27 mg (36 %) of 3-(2-pyridyl)-5-(3-cyano-5-(3-fluorophenyl)phenyl)-1,2,4-oxadiazole: ^1H NMR ($CDCl_3$): δ - 8.86 (d, 1H), 8.70 (s, 1H), 8.55 (s, 1H), 8.24 (d, 1H), 8.07 (s, 1H), 7.91 (t, 1H), 7.49 (m, 3H), 7.40 (m, 1H), 7.19 (m, 1H).

3-(2-pyridyl)-5-[5-(5-pyrimidyl)-pyrid-3-yl]-1,2,4-oxadiazole

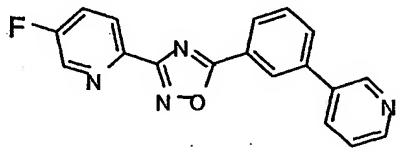
B123



In a similar fashion, 3-(2-pyridyl)-5-(5-bromo-pyrid-3-yl)-1,2,4-oxadiazole (42 mg, 0.1385 mmole), 5-pyrimidylboronic acid (26.6 mg,0.208 mmole) and $Pd(PPh_3)_4$ (23.99 mg, 0.021 mmole) in a solution of 2M sodium carbonate (1.5 mL) and ethylene glycol dimethyl ether (1.5 mL) was heated overnight at 105 °C. Standard workup afforded 3.2 mg (8%) of 3-(2-pyridyl)-5-[5-(5-pyrimidyl)-pyrid-3-yl]-1,2,4-oxadiazole (3.2 mg, 7.6 %).

3-(5-Fluoro-pyrid-2-yl)-5-[3-(3-pyridyl)phenyl]-1,2,4-oxadiazole

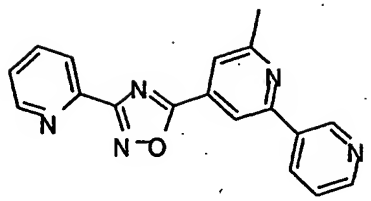
B225



A mixture of 3-(5-fluoro-pyrid-2-yl)-5-(3-bromophenyl)-1,2,4-oxadiazole (100 mg, 0.313 mmol), pyridine-3-boronic acid 1,3-propanediol cyclic ester (102 mg, 0.624 mmol), and tetrakis(triphenylphosphine)palladium(0) ($Pd(PPh_3)_4$, 50.8 mg, 0.044 mmol), in a solution of ethylene glycol dimethyl ether (2 mL) and 2M sodium carbonate (2 mL) was heated in a sealed vial at 110°C for 1 hour. The reaction was cooled, diluted with dichloromethane, washed with water and saturated brine, filtered, and concentrated. Silica gel chromatography using a gradient of 50% ethyl acetate in hexane to 100% ethyl acetate afforded 50 mg (50.2%) 3-(5-fluoro-pyrid-2-yl)-5-[3-(3-pyridyl)phenyl]-1,2,4-oxadiazole. ^{1}H-NMR ($CDCl_3$), δ (ppm): 8.91 (d, 1H), 8.69 (d, 1H), 8.64 (d, 1H), 8.49 (s, 1H), 8.28 (m, 2H), 8.00 (m, 1H), 7.84 (dd, 1H), 7.69 (t, 1H), 7.60 (td, 1H), 7.44(dd, 1H).

5-[3-Methyl-5-(3-pyridyl)-pyrid-4-yl]-3-(2-pyridyl)-1,2,4-oxadiazole

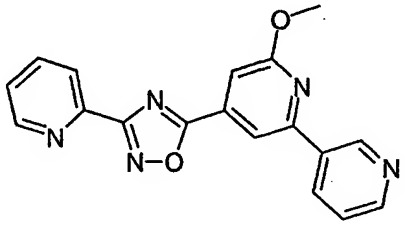
B226



A mixture of 5-(3-chloro-5-methyl-pyrid-4-yl)-3-(2-pyridyl)-1,2,4-oxadiazole (75 mg, 0.275 mmol), pyridine-3-boronic acid 1,3-propanediol cyclic ester (75 mg, 0.46 mmol), and tetrakis(triphenylphosphine)palladium(0) ($Pd(PPh_3)_4$, 30 mg, 0.026 mmol), in a solution of ethylene glycol dimethyl ether (1 mL) and 2M sodium carbonate (1 mL) was heated in a sealed vial at 100°C for 1 hour. The reaction was cooled, diluted with dichloromethane, washed with water and saturated brine, filtered, and concentrated. Silica gel chromatography using a gradient of 40% ethyl acetate in hexane to 100% ethyl acetate afforded 5.4 mg (7.4%) of 5-[3-methyl-5-(3-pyridyl)-pyrid-4-yl]-3-(2-pyridyl)-1,2,4-oxadiazole. ^{1}H-NMR ($CDCl_3$), δ (ppm): 9.32 (s, 1H), 8.87 (d, 1H), 8.70 (d, 1H), 8.30 (m, 2H), 8.25 (s, 1H), 8.00 (s, 1H), 7.90 (d, 1H), 7.47 (m, 2H), 2.77 (s, 3H).

5-[3-Methoxy-5-(3-pyridyl)-pyrid-4-yl]-3-(2-pyridyl)-1,2,4-oxadiazole

B227

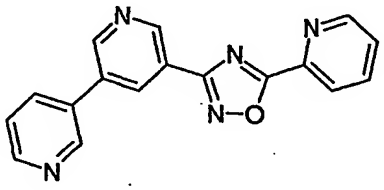


A mixture of 3-(2-pyridyl)-5-(3-chloro-5-methoxy-pyrid-4-yl)-1,2,4-oxadiazole (75 mg, 0.260 mmol), pyridine-3-boronic acid 1,3-propanediol cyclic ester (75 mg, 0.46 mmol), and tetrakis(triphenylphosphine)palladium(0) ($Pd(PPh_3)_4$, 30 mg, 0.026 mmol), in a solution of ethylene glycol dimethyl ether (1 mL) and 2M sodium carbonate (1 mL) was heated in a sealed vial at 100°C for 1 hour. The reaction was cooled, diluted with dichloromethane, washed with water and saturated brine, filtered, and concentrated. Silica gel chromatography using 40% ethyl acetate in hexane and 100% ethyl acetate afforded 3.5 mg (4.1%) 3-(2-pyridyl)-5-[3-

methoxy-5-(3-pyridyl)-pyrid-4-yl]-1,2,4-oxadiazole. ^{1}H-NMR ($CDCl_3$), δ (ppm): 9.39 (s, 1H), 8.91 (d, 1H), 8.72 (d, 1H), 8.42 (d, 1H), 8.25 (d, 1H), 8.20 (s, 1H), 7.92 (dt, 1H), 7.63 (dd, 1H), 7.50 (m, 2H), 4.12 (s, 3H).

5-(2-pyridyl)-3-[5-(3-pyridyl)-pyrid-3-yl]-1,2,4-oxadiazole

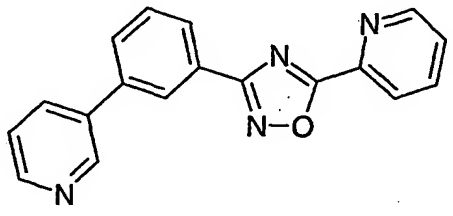
B228



A mixture of 3-(5-bromo-pyrid-3-yl)-5-(2-pyridyl)-1,2,4-oxadiazole 30.3 mg, 0.1 mmol), pyridine-3-boronic acid 1,3-propanediol cyclic ester (32.5 mg, 0.2 mmol), and tetrakis(triphenylphosphine)palladium(0) ($Pd(PPh_3)_4$, 15 mg, 0.013 mmol), in a solution of ethylene glycol dimethyl ether (1 mL) and 2M sodium carbonate (1 mL) was heated in a sealed vial at 100°C for 1 hour. The reaction was cooled, diluted with dichloromethane, washed with water and saturated brine, filtered, and concentrated. Silica gel chromatography using 50% ethyl acetate in hexane and 100% ethyl acetate afforded 13 mg (43.2%) 5-(2-pyridyl)-3-[5-(3-pyridyl)-pyrid-3-yl]-1,2,4-oxadiazole. ^{1}H-NMR ($CDCl_3$), δ (ppm): 9.49 (d, 1H), 9.01 (d, 1H), 8.93 (dd, 2H), 8.72 (t, 2H), 8.35 (d, 2H), 8.00 (dt, 1H), 7.59 (m, 1H), 7.47 (dd, 1H).

5-(2-pyridyl)-3-[3-(3-pyridyl)-phenyl]-1,2,4-oxadiazole

B229

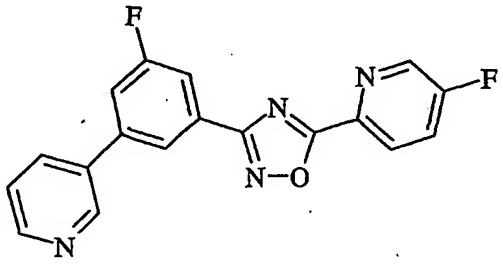


A mixture of 3-(3-iodophenyl)-5-(2-pyridyl)-1,2,4-oxadiazole (55 mg, 0.158 mmol), pyridine-3-boronic acid 1,3-propanediol cyclic ester (51.4 mg,

0.3152 mmol), and tetrakis(triphenylphosphine)palladium(0) ($Pd(PPh_3)_4$, 25 mg, 0.0216 mmol), in a solution of ethylene glycol dimethyl ether (1.5 mL) and 2M sodium carbonate (1.5 mL) was heated in a sealed vial at 100°C for 1 hour. The reaction was cooled, diluted with dichloromethane, washed with water and saturated brine, filtered, and concentrated. Silica gel chromatography using 40% and 60% ethyl acetate in hexane and then the treatment of 1M HCl (0.2 mL) afforded 29.4 mg (55.45%) 5-(2-pyridyl)-3-[3-(3-pyridyl)-phenyl]-1,2,4-oxadiazole hydrochloride. ^{1}H-NMR ($CDCl_3$), δ (ppm): 9.34 (s, 1H), 8.88 (m, 3H), 8.54 (s, 1H), 8.40 (d, 1H), 8.28 (d, 1H), 8.16 (d, 1H), 8.00 (m, 3H), 7.82 (m, 2H).

5-(5-Fluoro-pyrid-2-yl)-3-[3-fluoro5-(3-pyridyl)-phenyl]-1,2,4-oxadiazole

B230



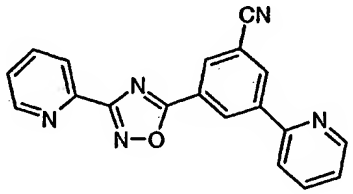
A mixture of 5-fluoro-picolinic acid hydrochloride (177.5 mg, 1 mmol) in dichloromethane (2 mL) was treated with 2M oxalyl chloride (2 ml, 4 mmol, dichloromethane). The mixture was stirred 2 hours at room temperature. The solvent and excess reagent were removed *in vacuo*. The residue was treated with 3-bromo-5-fluorophenyl-amidoxime (102 mg, 0.5 mmol) and triethylamine (404 mg, 4 mmol) in dichloromethane (2 mL). The mixture was then heated in dimethylformamide (1 mL) for 1 hours at 130 °C. Standard work up, afforded 80 mg (47%) of 3-(3-bromo-5-fluorophenyl)-5-(5-fluoro-pyrid-2-yl)-1,2,4-oxadiazole.

A mixture of 3-(3-bromo-5-fluorophenyl)-5-(5-fluoro-pyrid-2-yl)-1,2,4-oxadiazole (80 mg, 0.236 mmol), pyridine-3-boronic acid 1,3-propanediol cyclic ester (80 mg, 0.49 mmol), and tetrakis(triphenylphosphine)palladium(0) ($Pd(PPh_3)_4$, 40 mg, 0.0346 mmol), in a solution of ethylene glycol dimethyl ether (1.5 mL) and 2M sodium carbonate (1.5 mL) was heated in a sealed vial at 100°C for 1 hour.

The reaction was cooled, diluted with dichloromethane, washed with water and saturated brine, filtered, and concentrated. Silica gel chromatography using a gradient of 50 % ethyl acetate in hexane, afforded 14 mg (17.7%) 5-(5-fluoro-pyrid-2-yl)-3-[3-fluoro-5-(3-pyridyl)-phenyl]-1,2,4-oxadiazole. ^{1}H-NMR ($CDCl_3$), δ (ppm): 8.95 (s, 1H), 8.76 (d, 1H), 8.66 (d, 1H), 8.37 (dd, 2H), 8.25 (s, 1H), 7.95 (d, 2H), 7.43 (m, 2H).

3-(2-Pyridyl)-5-(3-cyano-5-(2-pyridyl)phenyl)-1,2,4-oxadiazole

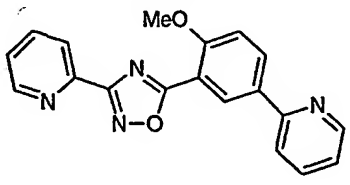
B124



A mixture of 3-(2-pyridyl)-5-(3-bromo-5-cyanophenyl)-1,2,4-oxadiazole (101 mg, 0.31 mmol), tetrakis(triphenylphosphine) palladium(0) ($Pd(PPh_3)_4$, 25 mg, 0.021 mmol) and tri-*n*-butyl(2-pyridyl)tin in tetrahydrofuran (2 mL) was heated overnight at 100 °C. The reaction mixture was cooled and transferred directly onto a flash silica column. Elution with a gradient of hexane:ethyl acetate:chloroform 3:1:4 to 2.5:1:4 followed by trituration with hexane in dichloromethane afforded 22 mg (22%) of 3-(2-pyridyl)-5-(3-cyano-5-(2-pyridyl)phenyl)-1,2,4-oxadiazole: ^{1}H NMR ($CDCl_3$): δ - 9.12 (s, 1H), 8.88 (d, 1H), 8.78 (d, 1H), 8.64 (s, 1H), 8.61 (s, 1H), 8.26 (d, 1H), 7.89 (m, 3H), 7.51 (m, 1H), 7.40 (m, 1H).

3-(2-Pyridyl)-5-[2-methoxy-5-(2-pyridyl)phenyl]-1,2,4-oxadiazole

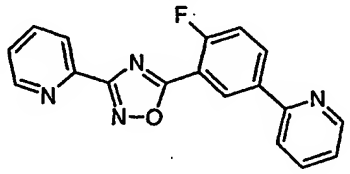
B125



In a similar fashion, a mixture of 3-(2-pyridyl)-5-(5-bromo-2-methoxyphenyl)-1,2,4-oxadiazole (110 mg, 0.331 mmol), pyridine-2-tributyltin (138.8 mg,0.663 mmole) and $Pd(PPh_3)_4$ (38.5 mg, 0.0333 mmole) in tetrahydrofuran (1 mL) was heated in a sealed vial overnight at 100 °C. Standard work up afforded 13.9 mg (13%) 3-(2-pyridyl)-5-[2-methoxy-5-(2-pyridyl)phenyl]-1,2,4-oxadiazole.

3-(2-Pyridyl)-5-[2-fluoro-5-(2-pyridyl)phenyl]-1,2,4-oxadiazole

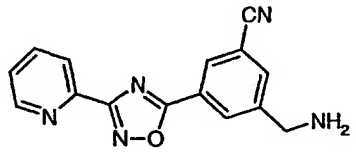
B126



In a similar fashion, 3-(2-pyridyl)-5-(5-bromo-2-fluorophenyl)-1,2,4-oxadiazole (100 mg, 0.312 mmol), pyridine-2-tributyltin (172 mg, 0.468 mmol) and $Pd(PPh_3)_4$ (36.1 mg, 0.0312 mmol) in tetrahydrofuran (1 mL) was heated in sealed vial overnight at 100 °C. Standard work up afforded 11.3 mg (11%) of 3-(2-pyridyl)-5-[2-fluoro-5-(2-pyridyl)phenyl]-1,2,4-oxadiazole.

3-(2-Pyridyl)-5-(3-aminomethyl-5-cyanophenyl)-1,2,4-oxadiazole

B127



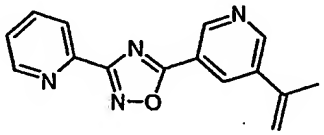
A mixture of 3-(2-pyridyl)-5-(3-cyano-5-methylphenyl)-1,2,4-oxadiazole (0.5 g, 1.91 mmol), *N*-bromosuccinimide (0.339 g, 1.91 mmol), and benzoyl peroxide (.0010 g, 0.04 mmol) in carbon tetrachloride (25 mL) was heated at 80 °C for 18 hours. After this time the reaction mixture was cooled and diluted with dichloromethane. The organic solution was washed with water and brine to afford 0.595 g (91%) of 3-(2-pyridyl)-5-(3-bromomethyl-5-cyanophenyl)-1,2,4-oxadiazole.

A solution of 3-(2-pyridyl)-5-(3-bromomethyl-5-cyanophenyl)-1,2,4-oxadiazole (0.5 g, 1.91 mmol) in dichloromethane (1.5 mL) was treated with a

0.5M ammonia (1.5 mL, 1.5 mmol, dioxane) and heated at 50 °C for 90 minutes. After this time the reaction mixture was cooled and diluted with dichloromethane. The organic solution was washed with water and brine. Silica gel chromatography of the crude product afforded 3.5 mg (5.5%) of 3-(2-pyridyl)-5-(3-aminomethyl-5-cyanophenyl)-1,2,4-oxadiazole.

3-(2-Pyridyl)-5-[5-(2-propenyl)-pyrid-3-yl]-1,2,4-oxadiazole

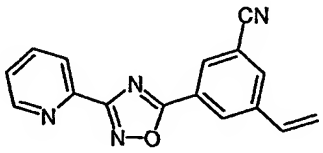
B128



Under an argon atmosphere, a solution of 5-bromonicotinic acid (1.01 g, 5 mmol) in tetrahydrofuran (10 mL) at −78 °C was treated dropwise with a 1.6M solution of n-butyllitium (6.99 ml, 11 mmol, hexane). After the reaction mixture was stirred for 15 minutes, acetone (1 mL) was added. The reaction mixture was then warmed to room temperature and quenched with 1*N* HCl. The solution was then concentrated *in vacuo*. The residue was treated with excess thionyl chloride (10 mL) and heated to 80 °C for 10 minutes. The excess thionyl chloride was then removed. The acid chloride in dichloromethane (10 mL) was treated with pyrid-2-ylamidoxime (0.685g, 5 mmol) and triethylamine (2.02 g, 20 mmoles) and stirred at room temperature for 15 minutes. *N,N*-Dimethylformamide (10 mL) was then added and the reaction mixture heated at 120 °C for 16 hours. The reaction was quenched by the addition of water and the precipitate collected and dried. Silica gel chromatograph of this material using 20% ethyl acetate in hexane afforded 153 mg (12%) of 3-(2-pyridyl)-5-[5-(2-propenyl)-pyrid-3-yl]-1,2,4-oxadiazole.

3-(2-Pyridyl)-5-(3-cyano-5-vinylphenyl)-1,2,4-oxadiazole

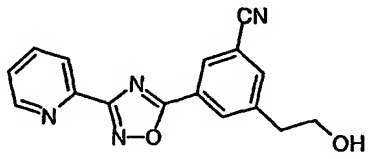
B129



A mixture of 3-(2-pyridyl)-5-(3-bromo-5-cyanophenyl)-1,2,4-oxadiazole (1.005 g, 3.21 mmol) and $Pd(PPh_3)_4$ (369 mg, 0.32 mmol) in tetrahydrofuran (10 mL) was treated with vinyl tributyl tin (0.985 mL, 3.36 mmol). The reaction mixture was heated in a sealed tube at 85 °C for 18 hours. After cooling, the mixture was diluted with dichloromethane and water. The organic layer was dried by filtration through an EX-TUBE. Silica gel chromatography afforded 691 mg (78%) of 3-(pyrid-2-yl)-5-(3-cyano-5-vinylphenyl)-1,2,4-oxadiazole: ^{1}H-NMR ($CDCl_3$), δ (ppm): (s, 1H), 8.52 (s, 1H), 8.43 (s, 1H), 8.23 (d, 1H), 7.90 (m, 2H), 7.48 (m, 1H), 6.78 (dd, 1H), 5.98 (d, 1H), 5.55 (d, 1H).

3-(2-Pyridyl)-5-(3-cyano-5-(2-hydroxyethyl)phenyl)-1,2,4-oxadiazole

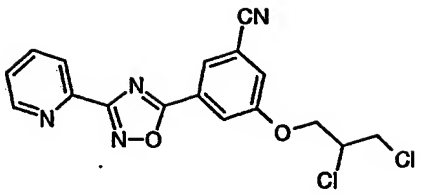
B130



A mixture of 3-(2-pyridyl)-5-(3-cyano-5-vinylphenyl)-1,2,4-oxadiazole (83 mg, 0.30 mmol) in dichloromethane (2 mL) was treated with 9-BBN dimer (40 mg, 0.16 mmol) and the reaction mixture stirred at room temperature for 4 hours. Sodium perborate tetrahydrate (157 mg, 1.02 mmol) and water (1 mL) were added and the resulting biphasic mixture was stirred vigorously for 18 hours. The mixture was diluted with dichloromethane and water and the organic layer dried by filtration through an EX-TUBE. Silica gel chromatography using a gradient of 20% to 75% ethyl acetate in hexane, followed by trituration in 10% ethyl acetate in hexane afforded 3.4 mg (3.7%) of 3-(2-pyridyl)-5-(3-cyano-5-(2-hydroxyethyl)phenyl)-1,2,4-oxadiazole: ^{1}H-NMR ($CDCl_3$), δ (ppm): 8.85 (d, 1H), 8.43 (s, 2H), 8.22 (d, 1H), 7.90 (t, 1H), 7.80 (s, 1H), 7.48 (m, 1H), 3.99 (m, 2H), 3.02 (t, 2H).

3-(2-Pyridyl)-5-(3-cyano-5-(2,3-dichloropropoxy)phenyl)-1,2,4-oxadiazole

B131



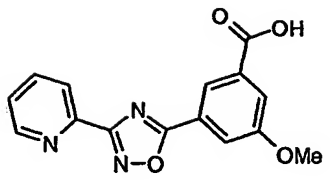
A stirred suspension of 3-(2-pyridyl)-5-(3-alloxy-5-(methoxycarbonyl)phenyl)-1,2,4-oxadiazole (160 mg, 0.47 mmol) in methanol (5 mL) at ambient temperature was treated with 1 M sodium hydroxide (0.8 mL, 0.80 mmol). The reaction was stirred 16 hours and solvent was removed *in vacuo*. The residue was dissolved in a small amount of water and then acidified with 1 *N* hydrogen chloride. Extraction of the aqueous phase with dichloromethane followed by concentration *in vacuo* afforded 104.5mg of 3-(2-pyridyl)-5-(3-alloxy-5-(hydroxycarbonyl)phenyl)-1,2,4-oxadiazole.

The carboxylic acid (104.5 mg, 0.32 mMol) was treated with excess thionyl chloride (2.5 mL) and the resulting mixture heated at reflux for 2 hours. The thionyl chloride was then removed in vacuo the acid chloride dissolved in chloroform (2.5 mL). The solution was cooled to 0 °C and treated with 2 M ammonia in methanol. The reaction mixture was then stirred at ambient temperature for additional 2 hours. After this time the reaction was filtered and concentrated to afford 86 mg of crude 3-(2-pyridyl)-5-(3-alloxy-5-(carboxamide)phenyl)-1,2,4-oxadiazole.

The intermediate benzamide (86 mg) was treated with thionyl chloride (2 mL) and heated in a sealed vial for 16 hours. The thionyl chloride was then removed *in vacuo*. The residue was dissolved in water followed by addition of 10 % sodium bicarbonate and the crude product extracted into ethyl acetate. Silica gel chromatography using a gradient of 30 % ethyl acetate in hexanes to 40 % ethyl acetate in hexanes afforded 15.4 mg (9%) of 3-(2-pyridyl)-5-(3-cyano-5-(2,3-dichloropropoxy)phenyl)-1,2,4-oxadiazole: ^{1}H NMR ($CDCl_3$): δ - 8.87 (d, 1H), 8.30 (m, 2H), 8.10 (s, 1H), 7.89 (m, 1H), 7.50 (m, 2H), 4.50 (m, 3H), 3.91 (m, 2H).

3-(2-Pyridyl)-5-(3-carboxy-5-methoxyphenyl)-1,2,4-oxadiazole

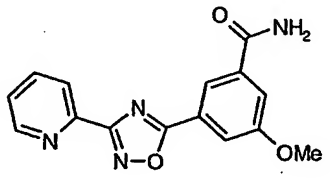
B132



A stirred suspension of 3-(2-pyridyl)-5-(3-methoxycarbonyl-5-methoxyphenyl)-1,2,4-oxadiazole (191.3 mg, 0.62 mmol) in methanol-tetrahydrofuran (1:1, 10 mL) was treated with 1 M sodium hydroxide (1.5 mL, 1.5 mmol). The reaction was stirred at 50°C for 5 hours and the solvent then removed *in vacuo*. The residue was dissolved in a small amount of water and then acidified (pH 4 – 5) by the addition of 2 *N* hydrogen chloride. The precipitate was collected and dried to afford 131.8 (72 %) of 3-(2-pyridyl)-5-(3-carboxy-5-methoxyphenyl)-1,2,4-oxadiazole: ^{1}H NMR (DMSO): δ - 8.81 (d, 1H), 8.28 (s, 1H), 8.21 (d, 1H), 8.06 (t, 1H), 7.88 (s, 1H), 7.74 (s, 1H), 7.65 (m, 1H), 3.95 (s, 3H).

3-(2-Pyridyl)-5-(3-(carboxamido)-5-methoxyphenyl)-1,2,4-oxadiazole

B133

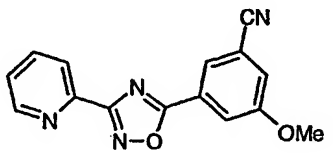


A solution of 3-(2-pyridyl)-5-(3-carboxy-5-methoxyphenyl)-1,2,4-oxadiazole (131.8 mg, 0.44 mMol) in thionyl chloride (2 mL) and a catalytic amount of *N,N*-dimethylformamide was heated at reflux for 2 hours. The excess thionyl chloride was then removed in vacuo and the intermediate acid chloride dissolved in chloroform (2 mL). After cooling to 0 °C the solution was then treated with 2 M ammonia in methanol (2 mL). The reaction mixture was then stirred at ambient temperature for 30 minutes. The precipitate was collected, washed with water and dried *in vacuo*. Silica gel chromatography of this material using a gradient of 50% ethyl acetate in hexane to 100 % ethyl acetate afforded 106.7 mg (81 %) of 3-(2-pyridyl)-5-(3-(carboxamido)-5-methoxyphenyl)-1,2,4-oxadiazole: ^{1}H NMR

(DMSO): δ - 8.81 (d, 1H), 8.31 (s, 2H), 8.22 (d, 1H), 8.08 (t, 1H), 7.80 (d, 2H), 7.66 (t, 2H), 3.95 (s, 3H).

3-(2-Pyridyl)-5-(3-cyano-5-methoxyphenyl)-1,2,4-oxadiazole

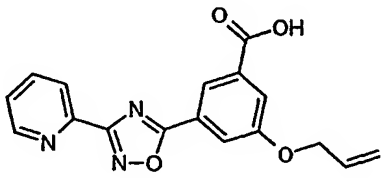
B134



A solution of 3-(2-pyridyl)-5-(3-(carboxamido)-5-methoxyphenyl)-1,2,4-oxadiazole (56.3 mg) in thionyl chloride (1.5 mL) was heated at reflux for 3 hours. The excess thionyl chloride was then removed in vacuo. Standard work up and silica gel chromatography using a mixture of hexanes, ethyl acetate, and dichloromethane (3.5:0.5:4) afforded 12.1 mg (23%) of 3-(2-pyridyl)-5-(3-cyano-5-methoxyphenyl)-1,2,4-oxadiazole: ^{1}H NMR ($CDCl_3$): δ - 8.86 (d, 1H), 8.23 (d, 1H), 8.16 (s, 1H), 8.02 (s, 1H), 7.92 (t, 1H), 7.50 (t, 1H), 7.40 (s, 1H), 4.04 (s, 3H).

3-(2-Pyridyl)-5-(3-allyloxy-5-carboxyphenyl)-1,2,4-oxadiazole

B135

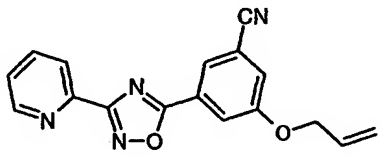


A stirred suspension of 3-(2-Pyridyl)-5-(3-allyloxy-5-(methoxycarbonyl)phenyl)-1,2,4-oxadiazole (1.8 g, 5.28 mmol) in methanol (40 mL) was treated with 1M sodium hydroxide (7.9 mL, 7.9 mmol) and the reaction stirred at ambient temperature for 36 hours. The solvent was removed *in vacuo*, and the residue was dissolved in water (30 mL) and then acidified (pH 4 – 5) by the addition of 2*N* hydrogen chloride. The resulting precipitate was collected and dried to afford 1.6 (94 %) of 3-(2-pyridyl)-5-(3-allyloxy-5-carboxyphenyl)-1,2,4-oxadiazole: ^{1}H NMR (DMSO): δ - 8.81 (d, 1H), 8.29 (s, 1H), 8.22 (d, 1H), 8.05

(m, 1H), 7.91 (s, 1H), 7.76 (s, 1H), 7.65 (m, 1H), 6.09 (m, 1H), 5.47 (dd, 1H), 5.33 (dd, 1H), 4.80 (d, 2H).

3-(2-Pyridyl)-5-(3-allyloxy-5-cyanophenyl)-1,2,4-oxadiazole

B136

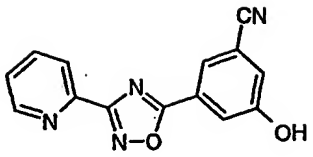


A solution of 3-(2-pyridyl)-5-(3-allyloxy-5-(carboxy)phenyl)-1,2,4-oxadiazole (1.2 g, 3.7 mmol) in thionyl chloride (24 mL), and a catalytic amount of *N,N*-dimethylformamide was heated at reflux for 1.5 hours. The thionyl chloride was then removed *in vacuo* and the acid chloride was dissolved in chloroform (20 mL). The solution was cooled to 0 °C and treated with a solution of 0.5M ammonia in dioxane (22 mL). The reaction mixture was then stirred at ambient temperature for 30 minutes. The resulting precipitate was collected and dried to afford 1.1 g of 3-(2-pyridyl)-5-(3-allyloxy-5-(carboxamide)phenyl)-1,2,4-oxadiazole.

A suspension of 3-(2-pyridyl)-5-(3-allyloxy-5-(carboxamide)phenyl)-1,2,4-oxadiazole (1.1 g, 3.6 mmol) in a dichloromethane at 0 °C was treated with pyridine (0.6 mL, 7.6 mmol) and then trifluoroacetic anhydride (0.636 mL, 4.5 mmol). The reaction was stirred at 0 °C for 20 minutes and then stirred overnight at ambient temperature. The reaction mixture was then washed with water and saturated brine, dried over anhydrous sodium sulfate, filtered and concentrated. Silica gel chromatography using a mixture of hexanes, ethyl acetate, and dichloromethane (3.5:0.5:1) afforded 1.0 g (91%) of 3-(2-pyridyl)-5-(3-allyloxy-5-cyanophenyl)-1,2,4-oxadiazole: ^{1}H NMR ($CDCl_3$): δ - 8.87 (d, 1H), 8.23 (d, 1H), 8.16 (s, 1H), 8.03 (s, 1H), 7.91 (t, 1H), 7.50 (m, 1H), 7.41 (s, 1H), 6.06 (m, 1H), 5.48 (dd, 1H), 5.38 (dd, 1H), 4.68 (d, 2H).

3-(2-Pyridyl)-5-(3-cyano-5-hydroxyphenyl)-1,2,4-oxadiazole

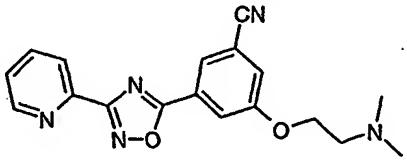
B137



A mixture of 3-(2-pyridyl)-5-(3-allyloxy-5-cyanophenyl)-1,2,4-oxadiazole (1.0 g, 3.4 mmol) and tetrabutylammonium iodide (1.4 g, 3.8 mmol) in dichloromethane (18 mL) at –78 °C, under argon, was treated with a solution of 1M boron trichloride in dichloromethane (22 mL, 22 mmol). After 5 minutes at –78 °C the reaction mixture was stirred at ambient temperature for 1 hour. The reaction was then quenched with ice water and stirred for 30 minutes. The mixture was then washed with saturated sodium bicarbonate and extracted with dichloromethane. The combined organic layers were dried over anhydrous sodium sulfate, filtered and concentrated. Silica gel chromatography using a gradient of 10% ethyl acetate in hexanes to 80% ethyl acetate in hexanes afforded 460 mg (51%) of 3-(2-pyridyl)-5-(3-cyano-5-hydroxyphenyl)-1,2,4-oxadiazole: ^{1}H NMR ($CDCl_3$/MeOD): δ - 8.81 (d, 1H), 8.23 (d, 1H), 8.01 (s, 1H), 7.95 (m, 1H), 7.92 (m, 1H), 7.54 (m, 1H), 7.35 (m, 2H).

3-(2-Pyridyl)-5-(3-cyano-5-(2-*N,N*-dimethylaminoethoxy)phenyl)-1,2,4-oxadiazole

B138

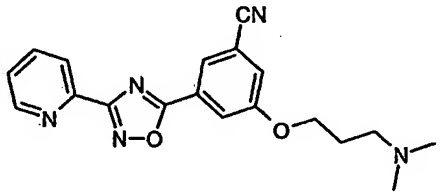


A mixture of 3-(2-pyridyl)-5-(3-cyano-5-hydroxyphenyl)-1,2,4-oxadiazole (30 mg, 0.11 mmol), potassium carbonate (374mg, 2.7 mmol) and 2-dimethylaminoethyl chloride hydrochloride (46 mg, 0.32 mmol) in *N,N*-dimethylformamide (1 mL) were heated in a sealed vial at 150 °C for 5 minutes. The reaction was cooled, diluted with dichloromethane, washed with water (3 x) and saturated brine, filtered and concentrated. Silica gel chromatography using a gradient of 1% methanol in dichloromethane to 5% methanol in dichloromethane

afforded 24 mg (53%) of 3-(2-pyridyl)-5-(3-cyano-5-(2-dimethylaminoethoxy)phenyl)-1,2,4-oxadiazole: ^{1}H NMR ($CDCl_3$): δ - 8.86 (d, 1H), 8.23 (d, 1H), 8.15 (s, 1H), 8.04 (s, 1H), 7.91 (t, 1H), 7.49 (m, 1H), 7.43 (s, 1H), 4.20 (t, 2H), 2.80 (t, 2H), 2.37 (s, 6H).

3-(2-Pyridyl)-5-(3-cyano-5-(N,N-dimethylaminopropoxy)phenyl)-1,2,4-oxadiazole

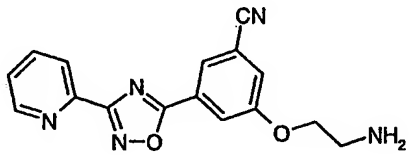
B139



In a similar fashion, 3-(2-pyridyl)-5-(3-cyano-5-hydroxyphenyl)-1,2,4-oxadiazole (31 mg, 0.12 mmol), potassium carbonate (381mg, 2.8 mmol) and 2-dimethylaminopropyl chloride hydrochloride (51 mg, 0.32 mmol) in *N,N*-dimethylformamide (1 mL) were heated in a sealed vial at 150°C for 5 minutes. Standard work up and chromatography afforded 10 mg (24 %) of 3-(2-pyridyl)-5-(3-cyano-5-(dimethylaminopropoxy)phenyl)-1,2,4-oxadiazole: ^{1}H NMR ($CDCl_3$): δ - 8.86 (d, 1H), 8.23 (d, 1H), 8.14 (s, 1H), 8.03 (s, 1H), 7.91 (t, 1H), 7.49 (m, 1H), 7.41 (s, 1H), 4.17 (t, 2H), 2.49 (t, 2H), 2.28 (s, 6H), 2.02 (q, 2H).

3-(2-Pyridyl)-5-(3-cyano-5-(2-aminoethoxy)phenyl)-1,2,4-oxadiazole

B140



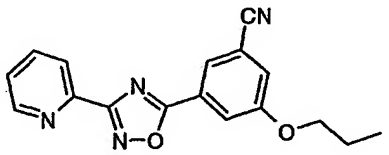
In a similar fashion, 3-(2-pyridyl)-5-(3-cyano-5-hydroxyphenyl)-1,2,4-oxadiazole (63 mg, 0.24 mmol), triphenylphosphine (100 mg, 0.38 mmol), *N*-(*tert*-butoxycarbonyl)ethanolamine (60 mg, 0.37 mmol) in tetrahydrofuran (2 mL) was treated with diethyl azodicarboxylate (0.060 mL, 0.38 mmol) dropwise and the

reaction mixture was stirred overnight. Standard work up and chromatography afforded the Boc-protected intermediate.

A solution of the Boc-protected intermdeiate in dichloromethane (2 mL) was treated with trifluoroacetic acid (1 mL) at 0 °C. After stirring for 1.5 hours, saturated sodium bicarbonate was added to the reaction mixture and the crude product extracted with dichloromethane. Silica gel column chromatography using a gradient of 1% methanol in dichloromethane to 10% methanol in dichloromethane afforded 27 mg (37%) of 3-(2-pyridyl)-5-(3-cyano-5-(2-aminoethoxy)phenyl)-1,2,4-oxadiazole: ^{1}H NMR ($CDCl_3$/MeOD): δ - 8.85 (d, 1H), 8.23 (d, 1H), 8.17 (s, 1H), 8.04 (s, 1H), 7.93 (t, 1H), 7.49 (m, 1H), 7.44 (s, 1H), 4.17 (t, 2H), 3.17 (m, 2H).

3-(2-Pyridyl)-5-(3-cyano-5-propoxyphenyl)-1,2,4-oxadiazole

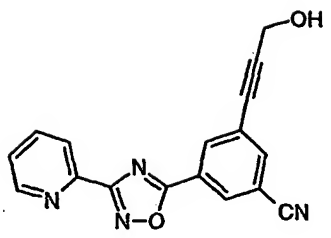
B141



A mixture of 3-(2-pyridyl)-5-(3-cyano-5-hydroxyphenyl)-1,2,4-oxadiazole (20 mg, 0.077 mmol), potassium carbonate (107 mg, 0.77 mmol) and propyl iodide (0.023 mL, 0.23 mmol) in *N,N*-dimethylformamide (1 mL) were heated in a sealed vial at 150 °C for 5 minutes. After cooling the reaction was diluted with dichloromethane, washed with water (3 times) and saturated brine, filtered and concentrated. Silica gel chromatography using a mixture of hexanes, ethyl acetate, and dichloromethane (3.5:0.5:4) followed by trituration with diethyl ether and hexanes afforded 9 mg (40 %) of 3-(2-pyridyl)-5-(3-cyano-5-propoxyphenyl)-1,2,4-oxadiazole: ^{1}H NMR ($CDCl_3$): δ - 8.86 (d, 1H), 8.23 (d, 1H), 8.14 (s, 1H), 8.00 (s, 1H), 7.91 (t, 1H), 7.49 (m, 1H) 7.39 (s, 1H), 4.06 (t, 2H), 1.88 (m, 2H), 1.08 (t, 3H).

3-(2-Pyridyl)-5-(5-cyano-3-[3-hydroxypropyn-1-yl]phenyl)-1,2,4-oxadiazole

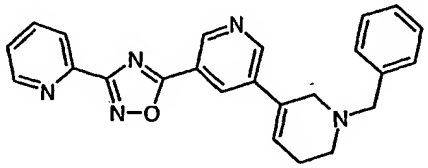
B142



A mixture of the 3-(2-pyridyl)-5-(5-cyano-3-iodophenyl)-1,2,4-oxadiazole (140 mg, 0.374 mmol), $Pd(PPh_3)_4$ (10 mg, 0.009), and CuI (30 mg, 0.158 mmol) in *N,N*-dimethylformamide (3 mL) was treated with triethylamine (1 mL, 726 mg, 7 mmol). The reaction mixture was cooled to 0 °C and treated with propargyl alcohol (56 mg, 1 mmol). The mixture was stirred at ambient temperature 5 hours and then filtered through a short plug of silica gel, washing with ethyl acetate. The organic solution was concentrated *in vacuo*. Silica gel chromatography afforded 20 mg (18%) of 3-(2-pyridyl)-5-(5-cyano-3-[3-hydroxypropyn-1-yl]phenyl)-1,2,4-oxadiazole: 1H-NMR (MeOH-d_4), δ ppm: 8.80 (d, 1H), 8.60 (s, 1H), 8.58 (s, 1H), 8.30 (d, 1H), 8.10 (m, 2H), 7.60 (m, 1H), 4.5 (s, 2H).

3-(2-Pyridyl)-5-[5-(3-*N*-benzyl-1,2,5,6-tetrahydropyridine)-pyrid-3-yl]-1,2,4-oxadiazole

B143



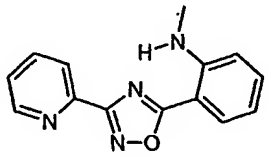
A mixture of 5-bromonicotinic acid (1.01 g, 5 mmoles) in tetrahydrofuran (10 ml), under an argon atmophere, was cooled to –78 °C and treated dropwise with a solution of 1.6M n-butyllithium (6.99 mL, 11 mmole, hexane). The reaction mixture was stirred for 15 minutes at –78 °C, and then treated with *N*-benzyl-3-piperidinone (1.89g, 10 mmoles). The reaction mixture was then allowed to warm to room temperature where it was quenched by the addition of 1*N* HCl. The reaction mixture was concentrated to dryness in vacuo. The residue was treated with thionyl chloride (10 mL) and the mixture heated for 10 minutes at 80 °C. The

excess thionyl chloride was removed *in vacuo*, and the residue treated with ethanol. Silica gel chromatograph using 1% methanol in dichloromethane afforded 120 mg (8%) of the nicotinic ethyl ester intermediate. Hydrolysis of the ester to the corresponding acid was accomplished using 1*N* sodium hydroxide (1 mL) and methanol (2 mL).

Activation of the intermediate acid using oxalyl chloride followed by treatment with pyrid-2-ylamidoxime (120 mg, 0.876 mmoles) and triethylamine (0.404 g, 4 mmol) in dichloromethane (10 mL) followed by heating at 120 °C in *N,N*-dimethylformamide (2 mL) for 4 hours, afforded, after standard work up 14.5 mg (10%) of 3-(2-pyridyl)-5-[5-(3-*N*-benzyl-1,2,3,6-tetrahydropyridine)-pyrid-3-yl]-1,2,4-oxadiazole.

3-(2-Pyridyl)-5-(2-*N*-methylaminophenyl)-1,2,4-oxadiazole

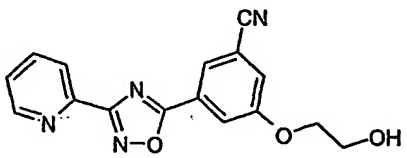
B144



A mixture of *N*-methyl-isatoic acid anhydride (177.2 mg, 1 mmol) and pyrid-2-ylamidoxime (137.14 mg, 1 mmol) in toluene (2 mL) was heated to 120 °C for 5 hours. After cooling, the solid was filtered, dissolved in ethylene glycol (1 mL) and heated at 125 °C for 6 hours. The solution was poured into water. Collection of the solid by filtration afforded 54 mg (21%) 3-(2-pyridyl)-5-(2-*N*-methylaminophenyl)-1,2,4-oxadiazole.

3-(2-Pyridyl)-5-(3-cyano-5-(2-hydroxyethoxy)phenyl)-1,2,4-oxadiazole

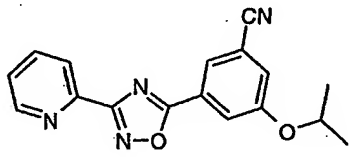
B231



A mixture of 3-(2-pyridyl)-5-(3-cyano-5-hydroxyphenyl)-1,2,4-oxadiazole (40 mg, 0.15 mmol), potassium carbonate (42 mg, 0.30 mmol) and bromoethane (30 mg, 0.23 mmol) in *N,N*-dimethylformamide (1 mL) was heated in a sealed vial at 100 °C for 2 hours. The reaction was cooled, diluted with dichloromethane, washed with water (3 x) and saturated brine, filtered and concentrated. Silica gel chromatography using 2% methanol in dichloromethane afforded 18 mg (39%) of 3-(2-pyridyl)-5-(3-cyano-5-(2-hydroxyethoxy)phenyl)-1,2,4-oxadiazole: ^{1}H NMR ($CDCl_3$/MeOD), δ (ppm): 8.80 (d, 1H), 8.27 (d, 1H), 8.17 (s, 1H), 8.07 (s, 1H), 8.00 (t, 1H), 7.58 (m, 1H), 7.53 (s, 1H), 4.24 (t, 2H), 3.99 (t, 2H).

3-(2-Pyridyl)-5-(3-cyano-5-isopropoxyphenyl)-1,2,4-oxadiazole

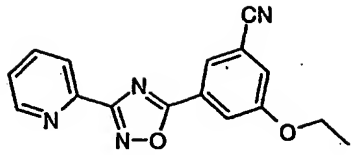
B232



A mixture of 3-(2-pyridyl)-5-(3-cyano-5-hydroxyphenyl)-1,2,4-oxadiazole (30 mg, 0.12 mmol), potassium carbonate (32 mg, 0.23 mmol) and 2-iodopropane (17 µL, 0.17 mmol) in *N,N*-dimethylformamide (1 mL) was heated in a sealed vial at 90 °C for 2 hours. The reaction was cooled, diluted with dichloromethane, washed with water (3 x) and saturated brine, filtered and concentrated. Silica gel chromatography using a hexanes/ethyl acetate/dichloromethane (3.5:0.5:4) afforded 24 mg (68%) of 3-(2-pyridyl)-5-(3-cyano-5-isopropoxyphenyl)-1,2,4-oxadiazole: ^{1}H NMR ($CDCl_3$), δ (ppm): 8.86 (d, 1H), 8.23 (d, 1H), 8.12 (s, 1H), 7.98 (s, 1H), 7.91 (m, 1H), 7.49 (m, 1H), 7.36 (s, 1H), 4.71 (m, 1H), 1.41 (m, 6H).

3-(2-Pyridyl)-5-(3-cyano-5-ethoxyhenyl)-1,2,4-oxadiazole

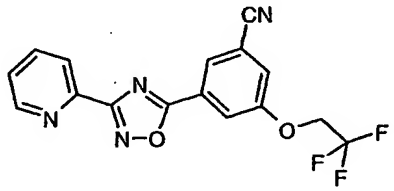
B233



A mixture of 3-(2-pyridyl)-5-(3-cyano-5-hydroxyphenyl)-1,2,4-oxadiazole (25 mg, 0.095 mmol), potassium carbonate (26 mg, 0.19 mmol) and iodoethane (11 µL, 0.14 mmol) in *N,N*-dimethylformamide (1 mL) was heated in a sealed vial at 70 °C for 1 hour. The reaction was cooled, diluted with dichloromethane, washed with water (3 x) and saturated brine, filtered and concentrated. Silica gel chromatography of the residue using hexanes/ethyl acetate/dichlrormethane (3.5:0.5:4) followed by trituration with diethyl ether afforded 11 mg (39%) of 3-(2-pyridyl)-5-(3-cyano-5-ethoxyphenyl)-1,2,4-oxadiazole: ^{1}H NMR ($CDCl_3$), δ (ppm): 8.86 (d, 1H), 8.23 (d, 1H), 8.14 (s, 1H), 7.99 (s, 1H), 7.91 (m, 1H), 7.49 (m, 1H), 7.38 (s, 1H), 4.17 (q, 2H), 1.49 (t, 3H).

3-(2-Pyridyl)-5-(3-cyano-5-(2,2,2-trifluoroethoxy)phenyl)-1,2,4-oxadiazole

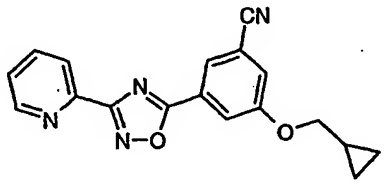
B234



A mixture of 3-(2-pyridyl)-5-(3-cyano-5-hydroxyphenyl)-1,2,4-oxadiazole (25 mg, 0.095 mmol), potassium carbonate (53 mg, 0.38 mmol) and 2-iodo-1,1,1-trifluoroethane (28 µL, 0.28 mmol) in *N,N*-dimethylformamide (1 mL) was heated in a sealed vial at 150 °C for 5 minutes hour. The reaction was cooled, diluted with dichloromethane, washed with water (3 x) and saturated brine, filtered and concentrated. Silica gel chromatography of the residue using hexanes/ethyl acetate/dichlrormethane (3.5:0.5:4) afforded 9 mg (27%) of 3-(2-pyridyl)-5-(3-cyano-5-(2,2,2-trifluoroethoxy)phenyl)-1,2,4-oxadiazole: ^{1}H NMR ($CDCl_3$), δ (ppm): 8.87 (d, 1H), 8.27 (s, 1H), 8.24 (d, 1H), 8.08 (s,1H), 7.92 (t, 1H), 7.50 (m, 2H), 4.53 (q, 2H).

3-(2-Pyridyl)-5-(3-cyano-5-cyclopropylmethoxyphenyl)-1,2,4-oxadiazole

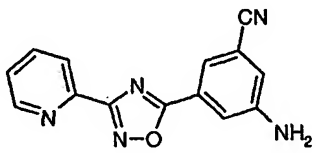
B235



A mixture of 3-(2-pyridyl)-5-(3-cyano-5-hydroxyphenyl)-1,2,4-oxadiazole (25 mg, 0.095 mmol), potassium carbonate (26 mg, 0.19 mmol) and (bromomethyl)cyclopropane (14 µL, 0.14 mmol) in *N,N*-dimethylformamide (1 mL) was heated in a sealed vial at 90 °C for 2 hours. The reaction was cooled, diluted with dichloromethane, washed with water (3 x) and saturated brine, filtered and concentrated. Silica gel chromatography of the residue using hexanes/ethyl acetate/dichlrormethane (3.5:0.5:4) followed by trituration with diethyl ether afforded 12 mg (41%) of 3-(2-pyridyl)-5-(3-cyano-5-cylopropylmethoxyphenyl)-1,2,4-oxadiazole: ^{1}H NMR ($CDCl_3$), δ (ppm): 8.86 (d, 1H), 8.23 (d, 1H), 8.14 (s, 1H), 7.99 (s, 1H), 7.91 (t, 1H), 7.50 (m, 1H), 7.40 (s, 1H), 3.95 (d, 2H), 1.21 (m, 1H), 0.72 (m, 2H), 0.41 (m, 2H).

3-(2-Pyridyl)-5-(3-amino-5-cyanophenyl)-1,2,4-oxadiazole

B236

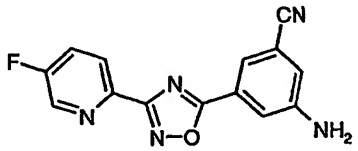


3-(2-Pyridyl)-5-(3-cyano-5-nitrophenyl)-1,2,4-oxadiazole (30 mg, 0.10 mmol) and tin(II) chloride dihydrate (115 mg, 0.51 mmol) in ethanol (1 mL) were sealed in a glass vial and then heated at 78 oC for 2 hours. The reaction was cooled and dichloromethane was added to the reaction mixture. The organic layer was washed with water and saturated brine, dried over anhydrous sodium sulfate, filtered, and concentrated. Silica gel chromatography of the residue using hexanes:ethyl acetate:dichloromethane 1:3:4 followed by recrystallization using

methanol afforded 2.8 mg (10%) of 3-(2-Pyridyl)-5-(3-amino-5-cyanophenyl)-1,2,4-oxadiazole: ^{1}H NMR ($CDCl_3$), δ (ppm): 8.85 (d, 1H), 8.22 (d, 1H), 7.91 (m, 2H), 7.78 (s, 1H), 7.48 (m, 1H), 7.11 (s, 1H), 4.17 (bs, 2H).

3-(5-fluoropyrid-2-yl)-5-(3-amino-5-cyanophenyl)-1,2,4-oxadiazole

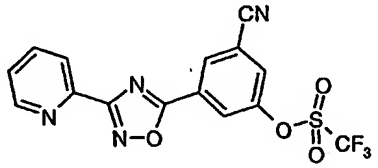
B237



3-(5-fluoropyrid-2-yl)-5-(3-cyano-5-nitrophenyl)-1,2,4-oxadiazole (30 mg, 0.096 mmol) and tin(II) chloride dihydrate (109 mg, 0.48 mmol) in ethanol (1 mL) were sealed in a glass vial and then heated at 78 oC for 2 hours. The reaction was cooled and dichloromethane was added to the reaction mixture. The organic layer was washed with water and saturated brine, dried over anhydrous sodium sulfate, filtered, and concentrated. Silica gel chromatography of the residue using hexanes:ethyl acetate:dichloromethane 1:3:4 followed by recrystallization using methanol afforded 6.3 mg (23%) of 3-(5-fluoropyrid-2-yl)-5-(3-amino-5-cyanophenyl)-1,2,4-oxadiazole: 1H NMR (CDCl3), δ (ppm): 8.69 (d, 1H), 8.25 (m, 1H), 7.89 (s, 1H), 7.76 (s, 1H), 7.61 (m, 1H), 7.11 (s, 1H), 4.17 (bs, 2H).

3-(2-Pyridyl)-5-(3-cyano-5-(trifluoromethylsulfonyloxy)phenyl)-1,2,4-oxadiazole

B238

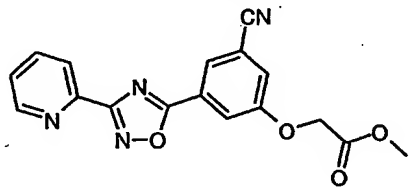


Trifluoromethanesulfonic anhydride (22.9 µL, 0.14 mmol) and triethylamine (23.7 µL, 0.17) were added under argon to a vial containing 3-(2-pyridyl)-5-(3-cyano-5-hydroxyphenyl)-1,2,4-oxadiazole (30 mg, 0.11 mmol) in dichloromethane (1 mL). The vial was then sealed and the reaction was left stirring overnight at ambient temperature. The reaction mixture was placed directly onto a flash column

and purified by eluting with hexanes:ethyl acetate:dichloromethane 3.5:0.5:4 to afford 11 mg (25%) of 3-(2-pyridyl)-5-(3-cyano-5-(trifluoromethylsulfonyloxy)phenyl)-1,2,4-oxadiazole: 1H NMR (CDCl3), δ (ppm): 8.88 (d, 1H), 8.63 (s, 1H), 8.44 (s, 1H), 8.24 (d, 1H), 7.93 (t, 1H), 7.83 (s, 1H), 7.52 (m, 1H).

3-(2-Pyridyl)-5-(3-cyano-5-(2-methoxy-2-oxoethoxy)phenyl)-1,2,4-oxadiazole

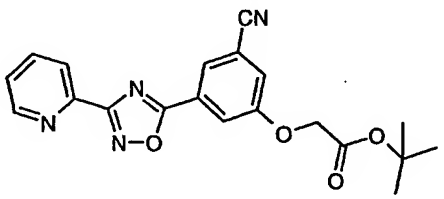
B239



A mixture of 3-(2-pyridyl)-5-(3-cyano-5-hydroxyphenyl)-1,2,4-oxadiazole (30 mg, 0.11 mmol), potassium carbonate (31 mg, 0.23 mmol) and methyl bromoacetate (16 µL, 0.17 mmol) in *N,N*-dimethylformamide (1 mL) was heated in a sealed vial at 100 °C for 2 hours. The reaction was cooled, diluted with dichloromethane, washed with water (3 x) and saturated brine, filtered and concentrated. Silica gel chromatography using hexanes:ethyl acetate:dichloromethane 3.5:0.5:4 followed by trituration with diethyl ether afforded 10 mg (26%) of 3-(2-pyridyl)-5-(3-cyano-5-(2-methoxy-2-oxoethoxy)phenyl)-1,2,4-oxadiazole: ^{1}H NMR ($CDCl_3$), δ (ppm): 8.87 (d, 1H), 8.23 (d, 1H), 8.22 (s, 1H), 8.01 (s, 1H), 7.92 (t, 1H), 7.50 (t, 1H), 7.42 (s, 1H), 4.81 (s, 2H), 3.86 (s, 3H).

3-(2-Pyridyl)-5-(3-cyano-5-(2-tert-butoxy-2-oxoethoxy)phenyl)-1,2,4-oxadiazole

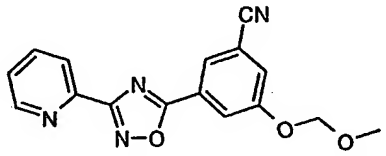
B240



A mixture of 3-(2-pyridyl)-5-(3-cyano-5-hydroxyphenyl)-1,2,4-oxadiazole (80 mg, 0.30 mmol), potassium carbonate (84 mg, 0.61 mmol) and *tert*-butylbromoacetate (67 µL, 0.46 mmol) in *N,N*-dimethylformamide (1 mL) was heated in a sealed vial at 90 °C for 1 hour. The reaction was cooled, diluted with dichloromethane, washed with water (3 x) and saturated brine, filtered and concentrated. Silica gel chromatography using hexanes:ethyl acetate:dichloromethane 3.5:0.5:4 afforded 62 mg (62%) 3-(2-pyridyl)-5-(3-cyano-5-(2-tert-butoxy-2-oxoethoxy)phenyl)-1,2,4-oxadiazole: ^{1}H NMR ($CDCl_3$), δ (ppm): 8.86 (d, 1H), 8.23 (d, 1H), 8.21 (s, 1H), 7.98 (s, 1H), 7.91 (t, 1H), 7.50 (t, 1H), 7.28 (s, 1H), 5.30 (s, 2H), 1.52 (s, 9H).

3-(2-Pyridyl)-5-(3-cyano-5-(methoxymethoxy)phenyl)-1,2,4-oxadiazole

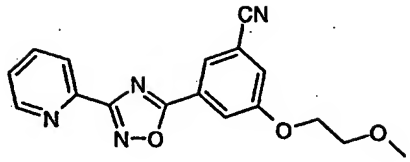
B241



A mixture of 3-(2-pyridyl)-5-(3-cyano-5-hydroxyphenyl)-1,2,4-oxadiazole (30 mg, 0.11 mmol), potassium carbonate (31 mg, 0.23 mmol) and chloromethyl methyl ether (26 µL, 0.34 mmol) in *N,N*-dimethylformamide (1 mL) was heated in a sealed vial at 70 °C for 2 hour. The reaction was cooled, diluted with dichloromethane, washed with water (3 x) and saturated brine, filtered and concentrated. Silica gel chromatography using 20 - 30% hexanes/ethyl acetate afforded 19 mg (54%) of 3-(2-Pyridyl)-5-(3-cyano-5-(methoxymethoxy)phenyl)-1,2,4-oxadiazole: ^{1}H NMR ($CDCl_3$), δ (ppm): 8.86 (d, 1H), 8.24 (d, 1H), 8.22 (s, 1H), 8.15 (s, 1H), 7.91 (t, 1H), 7.56 (s, 1H), 7.49 (m, 1H), 5.31 (s, 2H), 3.52 (s, 3H).

3-(2-Pyridyl)-5-(3-cyano-5-(2-methoxyethoxy)phenyl)-1,2,4-oxadiazole

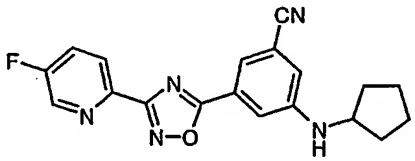
B242



A mixture of 3-(2-pyridyl)-5-(3-cyano-5-hydroxyphenyl)-1,2,4-oxadiazole (40 mg, 0.15 mmol), potassium carbonate (42 mg, 0.30 mmol) and 2-chloroethyl methyl ether (83 µL, 0.91 mmol) in *N,N*-dimethylformamide (1 mL) was heated in a sealed vial at 150 °C for 5 minutes. The reaction was cooled, diluted with dichloromethane, washed with water (3 x) and saturated brine, filtered and concentrated. Silica gel chromatography using hexanes:ethyl acetate:dichloromethane 1:1:2 followed by trituration with diethyl ether afforded 24 mg (50%) of 3-(2-pyridyl)-5-(3-cyano-5-(2-methoxyethoxy)phenyl)-1,2,4-oxadiazole: ^{1}H NMR ($CDCl_3$), δ (ppm): 8.87 (d, 1H), 8.23 (d, 1H), 8.17 (s, 1H), 8.04 (s, 1H), 7.91 (t, 1H), 7.49 (m, 1H), 7.45 (s, 1H), 4.27 (t, 2H), 3.81 (t, 2H), 3.48 (s, 3H).

3-(5-fluoropyrid-2-yl)-5-(3-cyano-5-cyclopentylaminophenyl)-1,2,4-oxadiazole

B243

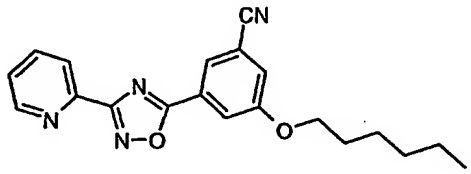


A mixture of 3-(5-fluoropyrid-2-yl)-5-(3-amino-5-cyanophenyl)-1,2,4-oxadiazole (30 mg, 0.11 mmol), cyclopentanone (24 µL, 0.26 mmol), sodium cyanoborohydride, 1.0 M solution in tetrahydrofuran, (128 µL, 0.12 mmol) in acetic acid (4 mL) was heated at 60 °C for 1 hour. After cooling, the reaction mixture was diluted with ethyl acetate and then washed with water (2X) and saturated brine, dried over anhydrous sodium sulfate, filtered, and concentrated. Silica gel chromatography using 20% ethyl acetate/hexanes afforded 15 mg (39%) of 3-(5-fluoropyrid-2-yl)-5-(3-cyano-5-cyclopentylaminophenyl)-1,2,4-oxadiazole: ^{1}H NMR ($CDCl_3$), δ (ppm): 8.69 (d, 1H), 8.25 (m, 1H), 7.79 (s, 1H), 7.61 (m, 2H), 6.99 (s,

1H), 4.17 (d, 1H), 3.88 (m, 1H), 2.10 (m, 1H), 1.74 (s, 2H), 1.50 (m, 1H), 1.27 (m, 2H), 0.87 (m, 2H).

3-(2-Pyridyl)-5-(3-cyano-5-hexyloxyphenyl)-1,2,4-oxadiazole

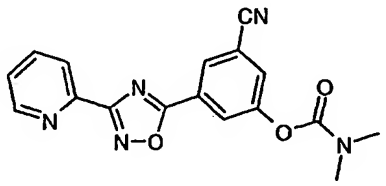
B244



A mixture of 3-(2-pyridyl)-5-(3-cyano-5-hydroxyphenyl)-1,2,4-oxadiazole (31 mg, 0.12 mmol), potassium carbonate (32 mg, 0.24 mmol) and hexyl bromide (25 µL, 0.18 mmol) in *N,N*-dimethylformamide (1 mL) was heated in a sealed vial at 90 °C for 35 minutes. The reaction was cooled, diluted with dichloromethane, washed with water (3 x) and saturated brine, filtered and concentrated. Silica gel chromatography using 2% methanol in dichloromethane afforded 18 mg (39%) of 3-(2-pyridyl)-5-(3-cyano-5-(2-hydroxyethoxy)phenyl)-1,2,4-oxadiazole: ^{1}H NMR ($CDCl_3$), δ (ppm): 8.86 (d, 1H), 8.23 (d, 1H), 8.13 (s, 1H), 8.00 (s, 1H), 7.91 (dd, 1H), 7.49 (dd, 1H), 7.38 (s, 1H), 4.09 (t, 2H), 1.84 (m, 2H), 1.49 (m, 2H), 1.37 (m, 4H), 0.93 (t, 3H).

3-(2-Pyridyl)-5-(3-cyano-5-(dimethylamino)carbonylphenyl)-1,2,4-oxadiazole

B245

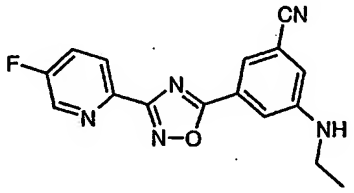


A mixture of 3-(2-pyridyl)-5-(3-cyano-5-hydroxyphenyl)-1,2,4-oxadiazole (39 mg, 0.15 mmol), potassium carbonate (32 mg, 0.30 mmol) and dimethylcarbamyl chloride (27 µL, 0.30 mmol) in *N,N*-dimethylformamide (1 mL) was heated in a sealed vial at 140 °C for 2 hours. The reaction was cooled, diluted with dichloromethane, washed with water (3 x) and saturated brine, filtered and

concentrated. Silica gel chromatography using hexanes:ethyl acetate:dichloromethane 3.5:0.5:4 afforded 3 mg (29%) of 3-(2-pyridyl)-5-(3-cyano-5-(dimethylamino)carbonylphenyl)-1,2,4-oxadiazole: ^{1}H NMR ($CDCl_3$), δ (ppm): 8.85 (d, 1H), 8.40 (s, 1H), 8.29 (s, 1H), 8.22 (d, 1H), 7.89 (m, 1H), 7.73 (s, 1H), 7.48 (dd, 1H), 3.14 (s, 3H), 3.06 (s, 3H).

3-(5-Fluoropyrid-2-yl)-5-(3-cyano-5-ethylaminophenyl)-1,2,4-oxadiazole

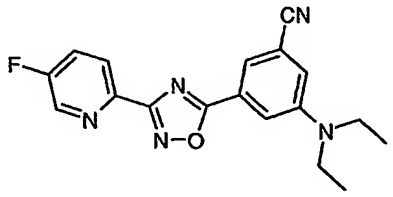
B246



A mixture of 3-(5-fluoropyrid-2-yl)-5-(3-cyano-5-nitrophenyl)-1,2,4-oxadiazole (30 mg, 0.11 mmol), potassium carbonate (29 mg, 0.21 mmol) and ethyl iodide (98 µL, 1.2 mmol) in *N,N*-dimethylformamide (1 mL) was heated in a sealed vial at 140 °C for 2 hours. The reaction was cooled, diluted with ethyl acetate, washed with water (3 x) and saturated brine, filtered and concentrated. Silica gel chromatography using hexanes:ethyl acetate:dichloromethane 3:1:4 afforded 6 mg (38%) of 3-(5-fluoropyrid-2-yl)-5-(3-cyano-5-ethylaminophenyl)-1,2,4-oxadiazole: ^{1}H NMR ($CDCl_3$), δ (ppm): 8.69 (d, 1H), 8.26 (dd, 1H), 7.80 (s, 1H), 7.61 (m, 2H), 6.99 (s, 1H), 4.12 (br, s, 1H), 3.26 (q, 2H), 1.32 (t, 3H).

3-(5-Fluoropyrid-2-yl)-5-(3-cyano-5-diethylaminophenyl)-1,2,4-oxadiazole

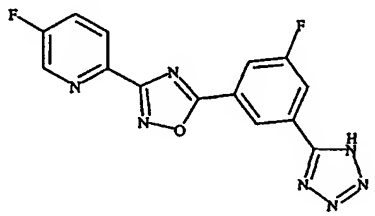
B247



A mixture of 3-(5-fluoropyrid-2-yl)-5-(3-cyano-5-nitrophenyl)-1,2,4-oxadiazole (30 mg, 0.11 mmol), potassium carbonate (29 mg, 0.21 mmol) and ethyl iodide

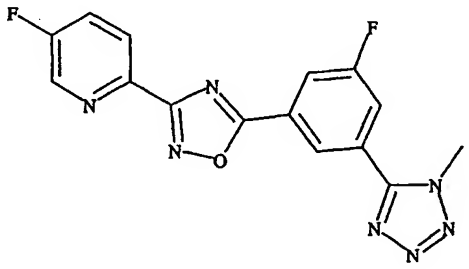
(98 µL, 1.2 mmol) in *N,N*-dimethylformamide (1 mL) was heated in a sealed vial at 140 °C for 2 hours. The reaction was cooled, diluted with ethyl acetate, washed with water (3 x) and saturated brine, filtered and concentrated. Silica gel chromatography using hexanes:ethyl acetate:dichloromethane 3:1:4 afforded 3 mg (20%) of 3-(5-fluoropyrid-2-yl)-5-(3-cyano-5-diethylaminophenyl)-1,2,4-oxadiazole: ^{1}H NMR ($CDCl_3$), δ (ppm): 8.69 (d, 1H), 8.27 (dd, 1H), 7.78 (s, 1H), 7.60 (m, 2H), 7.04 (s, 1H), 3.45 (q, 4H), 1.23 (t, 6H).

3-(5-Fluoro-pyrid-2-yl)-5-[3-fluoro-5-(1*H*-tetraazol-5-yl)-phenyl]-1,2,4-oxadiazole B248



To a mixture of 2 M trimethylaluminum (0.45 mL, 0.9 mmole, toluene) with toluene (1 mL) at 10 °C, trimethylsilyl azide (0.119 mL, 0.9 mmole) was added, followed by the addition of 5-(3-cyano-5-fluorophenyl)-3-(5-fluoro-pyrid-2-yl)-1,2,4-oxadiazole. The reaction was heated at 80 °C for 2 hours and then quenched with 6 N hydrochloride (2 mL) and solid was collected by filtration. The product was recrystallized with dimethylformamide to give 59 mg (36%) of 3-(5-fluoro-pyrid-2-yl)-5-[3-fluoro-5-(1*H*-tetraazol-5-yl)-phenyl]-1,2,4-oxadiazole. ^{1}H-NMR (DMSO-d6), δ (ppm): 8.83 (d, 1H), 8.70 (s, 1H), 8.31 (m, 1H), 8.10 (m, 2H), 8.04 (dt, 1H).

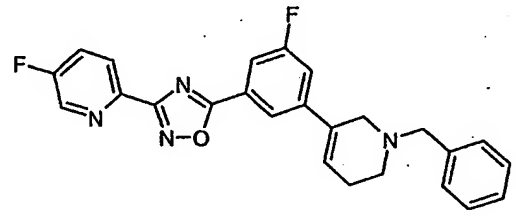
5-[3-Fluoro-5-(1-methyl-1*H*-tetraazol-5-yl)-phenyl]-3-(5-fluoro-pyrid-2-yl)-1,2,4-oxadiazole B249



To a solution of 3-(5-fluoro-pyrid-2-yl)-5-[3-fluoro-5-(1*H*-tetraazol-5-yl)-phenyl]-1,2,4-oxadiazole (30mg, 0.092 mmol) in tetrahydrofuran (1 mL), 0.5 M diazomethane (1 mL, 0.5 mmol, ether) was added. The reaction was quenched with water and extracted with dichloromethane. The product was purified by column chromatography with 20% ethyl acetate in hexanes to give 6.7 mg (21.4%) of 5-[3-fluoro-5-(1-methyl-1*H*-tetraazol-5-yl)-phenyl]-3-(5-fluoro-pyrid-2-yl)-1,2,4-oxadiazole. ^{1}H-NMR ($CDCl_3$), δ (ppm): 8.87 (s, 1H), 8.70 (d, 1H), 8.29 (dd, 1H), 8.10 (m, 2H), 7.62 (dt, 1H), 4.46 (s, 3H).

3-(5-Fluoro-2-pyridyl)-5-(3-(1-benzyl-1,2,5,6-tetrahydropyridin-3-yl)-5-fluorophenyl)-1,2,4-oxadiazole

B250

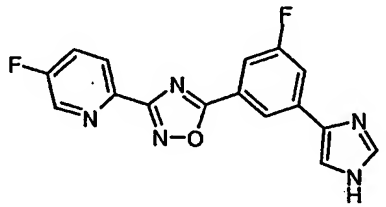


In a screw cap vial equipped with stir bar added 3-(5-Fluoro-2-pyridyl)-5-(3-fluoro-5-(3-pyridyl)phenyl)-1,2,4-oxadiazole (100 mg, 0.30 mmol), acetonitrile (2 ml) and benzyl bromide (0.05ml, 0.39 mmol). Stirred the resulting mixture at 90°C for 4h. Cooled the mixture to room temperature, concentrated *in-vacuo* and triturated the residue with 30% ethyl acetate in hexanes to isolate the quarternary salt. The isolated solid was dissolved in methanol (2 ml) and treated with sodium borohydride (22.6 mg, 0.60 mmol) at 0°C. The bright yellow reaction mixture was stirred at room temperature for 2 h. The reaction mixture was concentrated *in-vacuo* and the residue was dissolved in dichloromethane (20 ml). The organic phase was sequentially washed with water (20 ml) and brine (20 ml), dried (sodium sulfate), filtered and concentrated *in-vacuo*. The crude residue was purified on silica gel using 30% ethyl acetate in hexanes to isolate the title compound (10.1 mg, 8%) as yellow oil. ^{1}H-NMR ($CDCl_3$), δ (ppm): 8.69 (d, 1H), 8.26 (dd, 1H), 8.02

(s, 1H), 7.80 (dd, 1H), 7.60 (dt, 1H), 7.32 (m, 6H), 6.34 (m, 1H), 3.73 (s, 2H), 3.40 (bs, 2H), 2.63 (t, 2H), 2.39 (m, 2H).

3-(5-Fluoro-2-pyridyl)-5-(3-fluoro-5-(1*H*-imidazol-4-yl)phenyl)-1,2,4-oxadiazole

B251



A mixture of 3-Bromo-5-fluorobenzoic acid (0.41 g, 1.87 mmol) in dichloromethane (5 mL) was treated with oxalyl chloride (2.8 ml, 5.60 mmol, 2M dichloromethane) and 3 drops of *N,N*-dimethylformamide. The mixture was stirred 4 hours at room temperature. The solvent and excess reagent were removed *in-vacuo*. The residue was treated with 5-Fluoro-2-pyridylamidoxime (0.29 g, 1.87mmol) and triethylamine (0.78 ml, 5.60 mmol) in dichloromethane (5 mL). The mixture was then heated in dimethylformamide (5 mL) at 120°C, overnight. Standard work up followed by purification on silica gel using 20% ethyl acetate in hexanes afforded 3-(5-Fluoro-2-pyridyl)-5-(3-bromo-5-fluorophenyl)-1,2,4-oxadiazole (150 mg).

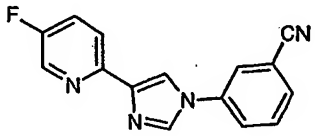
To the solution of 4-Tributylstannyl-1-trityl-1H-imidazole (106 mg, 0.18 mmol) in tetrahydrofuran (5 ml) added 3-(5-Fluoro-2-pyridyl)-5-(3-bromo-5-fluorophenyl)-1,2,4-oxadiazole (50.0 mg, 0.15 mmol) and tetrakis(triphenylphoshine)palladium (0) (17.1 mg, 0.01 mmol), sequentially. The resulting brownish yellow reaction mixture was heated at 100°C under argon overnight. The reaction mixture was cooled to room temperature and concentrated *in-vacuo*. The residue was purified on silica gel using 30% ethyl acetate in hexanes to isolate 3-(5-Fluoro-2-pyridyl)-5-(3-fluoro-5-(1-trityl-1*H*-imidazol-4-yl)phenyl)-1,2,4-oxadiazole (20.0 mg).

To a solution of 3-(5-Fluoro-2-pyridyl)-5-(3-fluoro-5-(1-trityl-1*H*-imidazol-4-yl)phenyl)-1,2,4-oxadiazole (20.0 mg, 0.04 mmol) in tetrahydrofuran (0.5 ml) added hydrochloric acid (0.14 ml, 2N aqueous). The resulting reaction mixture was

heated at reflux for 45 min. The reaction mixture was cooled to room temperature, diluted with ethyl acetate (30 ml), washed successively with sodium hydroxide (30 ml, 1N aqueous), water (30 ml) and brine (30 ml), dried (sodium sulfate), filtered and concentrated *in-vacuo.* The isolated residue was purified on silica gel using 5% methanol in dichloromethane to yield the title compound (1.7 mg) as a beige solid. ^{1}H-NMR ($CDCl_3$), δ (ppm): 9.64 (bs, 1H), 8.69 (d, 1H), 8.44 (s, 1H), 8.29 (dd, 1H), 7.81 (m, 3H), 7.61 (dt, 1H), 7.54 (s, 1H).

1-(3-Cyanophenyl)- 4-(5-fluoro-2-pyridyl)-1H-imidazole

B252



To a solution of 4-Iodo-1-trityl-1H-imidazole (5.0 g, 11.6 mmol) in dichloromethane (100 ml) added Ethylmagnesium bromide (3M in diethyl ether) (4.6 ml, 13.9 mmol). Stirred the reaction under argon atmosphere at room temperature for 1h. At this point added tributyltin chloride (4.1 ml, 13.9 mmol) to the reaction mixture and left the resulting mixture stirring at room temperature overnight. The reaction mixture was diluted with dichloromethane (100 ml), successively washed with saturated ammonium chloride (100 ml), water (100 ml) and brine (100 ml). The organic phase was dried (sodium sulfate), filtered and concentrated *in-vacuo* to yield 4-Tributylstannyl-1-trityl-1H-imidazole (2.35 g) as a white waxy solid.

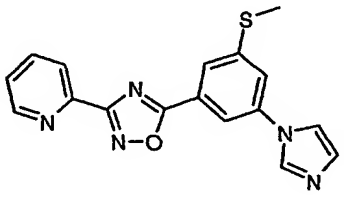
To the solution of 4-Tributylstannyl-1-trityl-1H-imidazole (1.00 g, 1.67 mmol) in toluene (10 ml) added 2-Chloro-5-fluoropyridine (0.31 g, 2.38 mmol) and tetrakis(triphenylphoshine)palladium (0) (0.19 g, 0.17 mmol), sequentially. The resulting brownish yellow reaction mixture was heated at reflux under argon overnight. The reaction mixture was cooled to room temperature and concentrated *in-vacuo*. The residue was purified on silica gel using 30% diethyl ether in hexanes to isolate 4-(5-Fluoro-2-pyridyl)-1-trityl-1H-imidazole (0.23 g) as a clear oil.

To a solution of 4-(5-Fluoro-2-pyridyl)-1-trityl-1H-imidazole (0.23 g, 0.56 mmol) in tetrahydrofuran (4 ml) added hydrochloric acid (2.4 ml, 2N aqueous). The resulting reaction mixture was heated at reflux for 45 min. The reaction mixture was cooled to room temperature and concentrated *in-vacuo*. The isolated residue was triturated with diethyl ether to yield 4-(5-Fluoro-2-pyridyl)imidazole (0.06 g) as the hydrochloride salt.

In a screw-cap vial, added 4-(5-Fluoro-2-pyridyl)imidazole (0.06 g, 0.30 mmol), 3-Fluorobenzonitrile (0.04 ml, 0.36 mmol), potassium carbonate (0.21 g, 1.5 mmol) and dimethylformamide (1 ml). Stirred the resulting reaction mixture at 110°C overnight. Cooled the reaction mixture to room temperature, diluted with chloroform (50 ml), sequentially washed with water (50 ml) and brine (50 ml). The organic phase was dried (sodium sulfate), filtered and concentrated *in-vacuo*. The crude residue was triturated with 10% diethyl ether in hexanes to yield the title compound (45 mg) as a dirty yellow colored solid. ^{1}H-NMR ($CDCl_3$), δ (ppm): 8.43 (d, 1H), 8.04 (dd, 1H), 7.93 (dd, 2H), 7.70 (m,4H), 7.48 (dt, 1H).

3-(2-Pyridyl)-5-(3-(1H-imidazol-1-yl)-5-thiomethoxyphenyl)-1,2,4-oxadiazole

B253

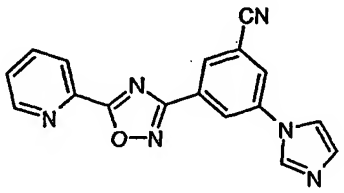


In a screw cap vial equipped with stir bar added 3-(2-Pyridyl)-5-(3-fluoro-5-thiomethoxyphenyl)-1,2,4-oxadiazole (20 mg, 0.07 mmol), potassium carbonate (17.5 mg, 0.13 mmol), imidazole (4.3 mg, 0.06 mmol) and dimethylformamide (1 ml). Stirred the resulting mixture at 150°C for 4 days. The reaction mixture was diluted with chloroform (30 ml) and washed with water (30 ml). The aqueous phase was re-extracted with chloroform (30 ml) and the combined organic phase was dried (sodium sulfate), filtered and concentrated *in-vacuo*. The crude residue was purified on silica gel using 2% methanol in dichloromethane to isolate the free

base of the desired compound. The free base was converted to it's hydrochloride salt (4.5 mg), yellow solid. ^{1}H-NMR (DMSO), δ (ppm): 9.64 (bs, 1H), 8.83 (d, 1H), 8.43 (s, 1H), 8.35 (s, 1H), 8.13 (m, 4H), 7.86 (bs, 1H), 7.70 (dt, 1H).

3-(3-Cyano-5-(1H-imidazol-1-yl)phenyl)-5-(2-pyridyl)-1,2,4-oxadiazole

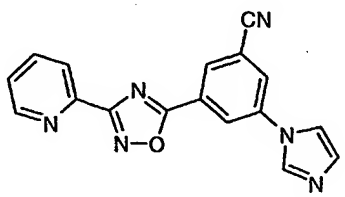
B254



In a screw cap vial equipped with stir bar added 3-(3-Cyano-5-fluorophenyl)-5-(2-Pyridyl)-1,2,4-oxadiazole (20 mg, 0.08 mmol), potassium carbonate (20.8 mg, 0.15 mmol), imidazole (7.7 mg, 0.11 mmol) and dimethylformamide (1 ml). Stirred the resulting mixture at 120°C for 2 h. The reaction mixture was diluted with chloroform (30 ml) and washed with water (30 ml). The aqueous phase was re-extracted with chloroform (30 ml) and the combined organic phase was dried (sodium sulfate), filtered and concentrated *in-vacuo*. The crude residue was purified on silica gel using 1% methanol in dichloromethane to isolate the free base of the desired compound as a white solid. The free base was converted to it's hydrochloride salt (11.7 mg), white solid. ^{1}H-NMR (DMSO), δ (ppm): 9.81 (s, 1H), 8.83 (m, 4H), 8.42 (m, 2H), 8.19 (dt, 1H), 7.92 (s, 1H), 7.80 (dd, 1H).

3-(2-Pyridyl)-5-(3-cyano-5-(1H-imidazol-1-yl)phenyl)-1,2,4-oxadiazole

B255

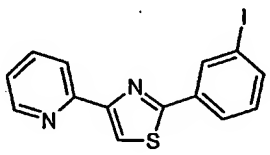


In a screw cap vial equipped with stir bar added 3-(2-Pyridyl)-5-(3-cyano-5-fluorophenyl)-1,2,4-oxadiazole (20 mg, 0.08 mmol), potassium carbonate (20.8 mg, 0.15 mmol), imidazole (7.7 mg, 0.11 mmol) and dimethylformamide (1 ml). Stirred the resulting mixture at 120°C for 2 h. The reaction mixture was diluted with chloroform (30 ml) and washed with water (30 ml). The aqueous phase was re-extracted with chloroform (30 ml) and the combined organic phase was dried (sodium sulfate), filtered and concentrated *in-vacuo*. The crude residue was purified on silica gel using 2% methanol in dichloromethane to isolate the free base of the desired compound as a white solid. The free base was converted to it's hydrochloride salt (10.0 mg), white solid. ^{1}H-NMR (DMSO), δ (ppm): 9.85 (s, 1H), 8.86 (m, 4H), 8.49 (s, 1H), 8.23 (d, 1H), 8.13 (t, 1H), 7.95 (s, 1H), 7.73 (dd, 1H).

EXAMPLE 8

2-(3-Iodophenyl)-4-(pyridin-2-yl)-1,3-thiazole

B145



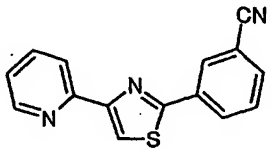
A suspension of 3-iodobenzoic acid (4.04 g, 16.2 mmol) in dichloromethane (30 mL) was treated with 2M oxalyl chloride (16 mL, 32 mmol, hexane) followed by two drops of *N,N*-dimethylformamide and stirred at ambient temperature for 2 hours. After this time the solvent was removed *in vacuo* and the residue dissolved in tetrahydrofuran (30 ml). The solution was cooled to 0 °C and treated with 2M ammonia (20 mL, 40 mmol, methanol) and the mixture stirred for 30 minutes. The mixture was then filtered and the solvent removed *in vacuo*. Recrystallization of the residue from methanol afforded 3.5 g (87%) of 3-iodobenzamide, as a white solid.

A mixture of 3-iodobenzamide (500 mg, 2.0 mmol) in toluene (5 mL) was treated with Lawesson's reagent (404 mg, 1 mmol) and the mixture heated at reflux for 16 hours. After cooling, silica gel chromatography afforded 260 mg (99% yield) of 3-iodothiobenzamide, as a yellow solid.

A solution of 2-bromoacetylpyridine (400 mg, 2.0 mmol) in ethanol (5 mL) was treated with 3-iodothiobenzamide (1.2g, 6 mmol) and the mixture heated at reflux for 16 hours. After cooling the mixture was concentrated *in vacuo*. Silica gel chromatography of the residue using a gradient of hexane to ethyl acetate afforded 302 mg (55 %) of 2-(3-iodophenyl)-4-(pyridin-2-yl)-1,3-thiazole, as a white solid.

2-(3-Cyanophenyl)-4-(pyridin-2-yl)-1,3-thiazole

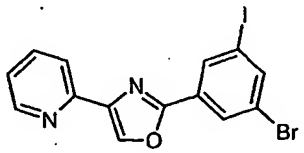
B146



A mixture of 2-(3-iodophenyl)-4-(pyridin-2-yl)-1,3-thiazole (130 mg, 0.36 mmol), zinc cyanide (117 mg, 1.0 mmol) and $Pd(PPh_3)_4$ (10 mg, 0.009 mmol) in *N,N*-dimethylformamide (2 mL) was heated overnight at 80 °C. The mixture was cooled and diluted with toluene (5 mL). The organic solution was washed with 2*N* NH_4OH (2 x 10 mL). The mixture was then extracted with ethyl acetate and the organic extract was washed with brine. The organic solution was dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo*. Silica gel chromatography afforded 28 mg (30 %) of 2-(3-cyanophenyl)-4-(pyridin-2-yl)-1,3-thiazole: 1H-NMR ($CDCl_3$), δ ppm: 8.65 (d, 1H), 8.38 (s, 1H), 8.25 (m, 2H), 8.15 (s, 1H), 7.85 (m, 1H), 7.72 (m, 1H), 7.6 (t, 1H), 7.28 (m, 1H). GC/EI-MS gave *m/z* 263 (M^+)

2-(3-Bromo-5-iodophenyl)-4-(pyridin-2-yl)-1,3-oxazole

B147

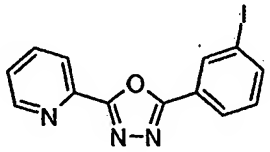


A solution of 2-bromoacetylpyridine (1.0 g, 5 mmol) in toluene (5 mL) was treated with 3-bromo-5-iodobenzamide (2.0 g, 6 mmol) and the mixture heated at

reflux for 60 hours. The mixture was then cooled and the solvent was removed *in vacuo*. Silica gel chromatography using a gradient of hexane to ethyl acetate afforded 10 mg (1 %) of 2-(3-bromo-5-iodophenyl)-4-(pyridin-2-yl)-1,3-oxazole: 1H-NMR ($CDCl_3$), δ ppm: 8.62 (d, 1H), 8.42 (m, 1H), 8.38 (s, 1H), 8.24 (m, 1H), 8.00 (t, 1H), 7.95 (d, 1H), 7.8 (m, 1H), 7.27 (m, 1H).

2-(2-Pyridyl)-5-(3-iodophenyl)-1,3,4-oxadiazole

B148

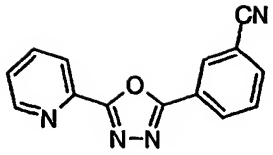


A mixture of picolinic acid (0.47g, 3.82mmol), 3-iodobenzhydrazide (1.00 g, 3.82 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (0.80 g, 4.20 mmol), and 4-dimethylaminopyridine (0.05 g, 0.38 mmol) in dichloromethane (10 mL) was stirred overnight at ambient temperature. After this time, the reaction mixture was diluted with dichloromethane (200 mL). The organic solution was washed sequentially with water (100 mL), saturated sodium bicarbonate (150 mL), water (100 mL) and brine (100 mL). The organic phase was dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo* to afford 0.33 g of the intermediate diacyl hydrazide.

The intermediate diacyl hydrazide.(0.15g, 0.41mmol) was then treated with phosphorus oxychloride (2 mL) and heated at 110°C for 40 minutes. After cooling the reaction was diluted with dichloromethane (10ml). The organic solution was washed sequentially with 1 *N* sodium hydroxide (10 mL), water (100 mL) and brine (100 mL). The organic phase was dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo*. Silica gel chromatography using 30% ethyl acetate in hexanes afforded 0.03 g (22%) of 2-(2-pyridyl)-5-(3-iodophenyl)-1,3,4-oxadiazole.

2-(2-Pyridyl)-5-(3-cyanophenyl)-1,3,4-oxadiazole

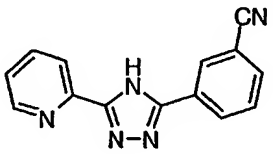
B149



Under an argon atmosphere, a mixture of 2-(2-pyridyl)-5-(3-iodophenyl)-1,3,4-oxadiazole (0.03 g, 0.08 mmol), zinc cyanide (0.01g, 0.12mmol), and $Pd(PPh_3)_4$ (9.1 mg, 0.01 mmol) in *N,N*-dimethylformamide (2ml) was heated at 80 °C for 2.5 hours. After cooling the reaction mixture was diluted with ethyl acetate and sequentially washed with water (3 x 50 mL) and brine (50 mL). The organic phase was dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo*. Recrystallization of the crude product from 5% ethyl acetate in hexanes, afforded 5.8 mg (30%) of 2-(2-pyridyl)-5-(3-cyanophenyl)-1,3,4-oxadiazole.

2-(2-Pyridyl)-5-(3-cyanophenyl)-1,3,4-triazole

B150

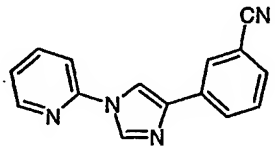


A solution of 3-cyanobenzoic acid (1.0 g, 6.80 mmol) in tetrahydrofuran (10 mL) at 0 °C was treated with triethylamine (2.84 mL, 20.4 mmol) and ethyl chloroformate (0.78 mL, 8.16 mmol) and stirred at 0 °C for 1h. The resulting white precipitate was removed by filtration and the filtrate cooled back to 0 °C. Hydrazine monohydrate (1.00 mL, 20.4 mmol) was added and the mixture stirred at ambient temperature for 3.5 hours. The reaction mixture was then concentrated to dryness *in vacuo* and the residue was dissolved in dichloromethane (150 mL). The organic phase was sequentially washed with water (100 mL), 1 *N* sodium hydroxide (100 mL), water (100 mL) and brine (100 mL). The organic phase was dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo*. Silica gel chromatography using 3% methanol in dichloromethane afforded 0.32 g (30%) of 3-cyanobenzhydrazide.

A solution of 2-cyanopyridine (0.18 mL, 1.86 mmol) in methanol (5 mL) was treated with sodium metal (12.8 mg, 0.56 mmol) a stirred at ambient temperature for 1 hour. The reaction mixture was then treated with a solution of 3-cyanobenzhyrazide (0.30 g, 1.86 mmol) in methanol (5 mL) and heated at reflux for 3 hours. The reaction mixture was then concentrated *in vacuo*. The resulting yellow solid was dissolved in toluene (2 mL) and heated overnight at 175 °C. The reaction mixture was concentrated *in vacuo*. Silica gel chromatography using 2% methanol in dichloromethane afforded 0.12 g (26%) of 2-(2-pyridyl)-5-(3-cyanophenyl)-1,3,4-triazole.

4-(3-Cyanophenyl)-1-(2-pyridyl)-1H-imidazole

B151



A mixture of 4-bromo-1-trityl-1H-imidazole (0.2g, 0.51mmol), 3-cyanophenylboronic acid (0.11g, 0.77mmol), and $Pd(PPh_3)_4$ (0.06g, 0.05mmol) in a solution of ethylene glycol dimethyl ether (2 mL) and 2M sodium carbonate (2 mL) was heated in a sealed vial overnight at 120 °C. After cooling, the reaction mixture was diluted with dichloromethane (30 mL) and washed with water (50 mL) and brine (30 mL). The organic phase was dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo*. Silica gel chromatography of the crude residue using 2% ethyl acetate in hexanes afforded 0.07 g (34%) 4-(3-cyanophenyl)-1-trityl-1H-imidazole as white foam.

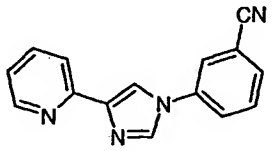
A solution of 4-(3-cyanophenyl)-1-trityl-1H-imidazole (0.07 g, 0.17 mmol) in tetrahydrofuran (1.36 mL) was treated with 2*N* hydrochloric acid (0.68 mL) and the resulting mixture was heated at reflux for 45 minutes. After cooling the reaction mixture was concentrated *in vacuo* and the residue dissolved in dichloromethane (20 mL). The organic phase was successively washed with 1*N* sodium hydroxide (10 mL), water (20 mL) and brine (20 mL). The organic solution was dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo*. Silica gel

chromatography of the residues using 3% methanol in dichloromethane afforded 0.02 g (72%) of 4-(3-cyanophenyl)imidazole as a white solid.

A solution of 4-(3-cyanophenyl)imidazole (0.02 g, 0.11 mmol) in *N*-methylpyrrolidinone (0.5 mL) was treated with 2-bromopyridine (1.05 mL, 11.1 mmol) and the reaction mixture heated overnight at 160°C. After cooling the reaction mixture was diluted with dichloromethane (40 mL) and the organic phase was successively washed with water (10 x 50 mL) and brine (50 mL). The organic phase was dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo*. Silica gel chromatography using 30% ethyl acetate in hexanes afforded 2.5mg (9%) of 4-(3-cyanophenyl)-1-(2-pyridyl)-1H-imidazole, as an off-white solid.

4-(2-Pyridyl)-1-(3-cyanophenyl)-1H-imidazole

B152



Under an argon atmosphere, a solution of 4-iodo-1-trityl-1H-imidazole (1.00 g, 2.29 mmol) in dichloromethane (10 mL) was treated with isopropylmagnesium bromide (2.75 mL of 1 M, 2.75 mmol, in tetrahydrofuran) and stirred at ambient temperature for 1 hour. After this time, the reaction was treated with tributyltin chloride (0.81 mL, 2.98 mmol) and the resulting mixture stirred overnight at ambient temperature. The reaction mixture was then diluted with dichloromethane (50 mL) and successively washed with saturated ammonium chloride (50 mL), water (50 mL) and brine (50 mL). The organic phase was dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo* to afford 1.37 g of crude 4-tributylstannyl-1-trityl-1H-imidazole.

The crude 4-tributylstannyl-1-trityl-1H-imidazole (1.37g) in toluene (10 mL) was treated sequentially with 2-bromopyridine (0.33 mL, 3.43 mmol) and $Pd(PPh_3)_4$ (0.26 g, 0.23 mmol). The reaction mixture was heated at reflux under an argon atmosphere for 4 hours. After cooling, the reaction mixture was concentrated *in vacuo*. The residue was dissolved in chloroform (50 mL) and sequentially washed

with aqueous saturated potassium fluoride (75 mL), water (75 mL) and brine (100 mL). The organic phase was dried over anhydrous sodium sulfate, filtered and concentrated *in-vacuo* to afford 0.69 g of crude 4-(2-pyridyl)-1-trityl-1H-imidazole.

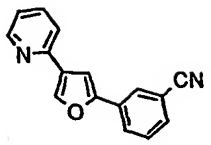
A solution of the crude 4-(2-pyridyl)-1-trityl-1H-imidazole (0.69g) in tetrahydrofuran (14 mL) was treated with 2 *N* hydrochloric acid (7.2 mL) and heated at reflux for 45 minutes. After cooling the reaction mixture was concentrated *in vacuo* and the residue was dissolved in dichloromethane (20 mL). The organic solution was successively washed with aqueous 1*N* sodium hydroxide (10 mL), water (20 mL) and brine (20 mL). The organic solution was then dried over anhydrous sodium sulfate, filtered, and concentrated *in-vacuo* to afford 0.12 g of crude 4-(2-pyridyl)imidazole, as a sticky white solid.

To a flame dried, argon purged screw-cap vial, containing copper (I) triflate.benzene complex (0.01 g, 0.03 mmol), 1,10-phenanthroline (0.10 g, 0.54 mmol), trans-dibenzylideneacetone (0.01 g, 0.03 mmol) and cesium carbonate (0.20g, 0.60mmol) was added a solution of 4-(2-pyridyl)imidazole (0.08 g, 0.54 mmol) and 3-iodobenzonitrile (0.19 g, 0.82 mmol) in *ortho*-xylene (2 mL). The resulting brownish black reaction mixture was heated overnight at 120°C. After cooling, the reaction mixture was diluted with dichloromethane (20 mL) and washed sequentially with saturated ammonium chloride (20 mL) and brine (20 mL). The organic phase was then dried with sodium sulfate, filtered, and concentrated *in vacuo*. Silica gel chromatography of the crude residue using 1% methanol (2 M in ammonia) in dichloromethane afforded 11 mg of 4-(2-pyridyl)-1-(3-cyanophenyl)-1H-imidazole, as an off-white solid.

EXAMPLE 9

3-(2-Pyridyl)-2-(3-cyanophenyl)-furan

B256



A solution of n-butyllithium (6.8 mL, 1.6M in hexanes, 11.0 mmol) was added in a dropwise manner to a solution of tetrahydro-2-(2-propynyloxy)-2H-pyran (1.43 mL, 10.0 mmol) in THF (30 mL) at -78 °C and the reaction mixture was stirred at -50°C for 30 min prior to the dropwise addition of 3-cyanobenzaldehyde (1.44 mL, 11.0 mmol) at -78°C. The resulting mixture was stirred for 30 min at -78°C. After the reaction mixture was warmed to room temperature, it was quenched by pouring over ice. The crude product was partitioned between ethyl acetate (450 mL) and sodium hydrogen sulfate (1M, aqueous). The organic layer was washed sequentially with water and brine, and dried over sodium sulfate. Removal of the solvent *in vacuo* yielded the crude product (2.87 g, 100%).

A solution of this crude product in dichloromethane (5 mL) was added to a mechanically stirred heterogenous mixture of manganese dioxide (9.660 g, 4.42 mol) in dichloromethane (25 mL) at 0 °C and stirred at this temperature for 1 hour. The reaction mixture was filtered through magnesium sulfate, and the solvent was removed *in vacuo* yielding the crude acetylenic ketone. Pyridinium-p-toluene sulfonate (220.0 mg) was added to a solution of the crude acetylenic ketone in ethanol (25 mL). The resulting mixture was stirred at 50 °C for 4 h. After allowing the mixture to cool to room temperature, it was diluted with ethyl acetate (80mL), washed sequentially with water (3x50mL) and brine (50mL), and dried over sodium sulfate. After removal of the solvent *in vacuo*, flash chromatography on silica gel (10%-20% ethyl acetate in hexanes) yielded the crude deprotected alcohol (793.1 mg, 30% over 2 steps).

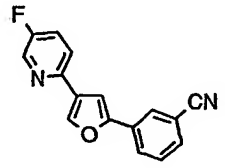
To a stirred solution of the deprotected alcohol (793.1 mg, 4.28 mmol) and dichloromethane (3 mL), HBr in acetic acid (30%, 1.69 mL) was added dropwise at 0°C. The reaction mixture was stirred for 1.5 h at 0 °C . The reaction mixture was diluted with ethyl acetate (50 mL) and then quenched by pouring it over ice, ether and sodium bicarbonate. The crude product was then taken into ethyl

acetate (300mL), washed sequentially with water, sodium sulfite and brine, and dried over sodium sulfate. The solvent was removed *in vacuo*. Flash chromatography on silica gel (0-5% ethyl acetate in hexane) yielded 1.5098 g (100% yield) of 3-bromo-2-(3-cyanophenyl)-furan. The oil was taken on to the next step without further purification.

A solution of 3-bromo-2-(3-cyanophenyl)-furan (112 mg, 0.45 mmol), pyridyl 2-trimethyl stannane (240 mg, 0.996 mmol) and $Pd(PPh_3)_4$ (20 mg, 0.02 mmol) in anhydrous toluene (5 mL) was stirred at 110°C for 3 days. After cooling to room temperature, the product was filtered through 1g SPE tube and washed through with dichloromethane (50mL), and the solvent was removed *in vacuo*. Flash chromatography on silica gel (15-50% ethyl acetate in hexanes) yielded 32.4 mg (42%, GC/MS RT 9.209 min, 100%pure) of 3-(2-pyridyl)-2-(3-cyanophenyl)-furan. ^{1}H-NMR ($CDCl_3$), δ (ppm): 8.61 (d, 1H), 8.07 (s, 1H), 7.99 (s, 1H), 7.92 (m, 1H), 7.71 (m, 1H), 7.53 (m, 3H), 7.27 (s, 1H), 7.19 (m, 1H).

3-(5-fluoro-2-pyridyl)-2-(3-cyanophenyl)-furan

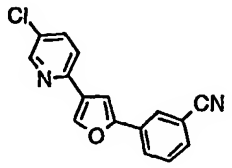
B257



In a similar fashion, a solution of 3-bromo-2-(3-cyanophenyl)-furan (110 mg, 0.44 mmol), 5-fluoro-pyridyl 2-trimethyl stannane (172 mg, 0.66 mmol) and $Pd(PPh_3)_4$ (20 mg, 0.02 mmol) in anhydrous toluene (5 mL) was stirred at 110°C for 3 days. After cooling to room temperature, the product was filtered through 1g SPE tube and washed through with dichloromethane (50mL), and the solvent was removed *in vacuo*. Chromatography (5g silica SPE tube, 10% ethyl acetate in hexanes) yielded 29.3 mg (35%, GC/MS RT 9.029, 97%pure) of 3-(5-fluoro-2-pyridyl)-2-(3-cyanophenyl)-furan. ^{1}H-NMR ($CDCl_3$), δ (ppm): 8.47 (d, 1H), 8.05 (s, 1H), 8.01 (s, 1H), 7.92 (dd, 1H), 7.40-7.57 (m, 5H), 7.21 (s, 1H).

3-(5-chloro-2-pyridyl)-2-(3-cyanophenyl)-furan

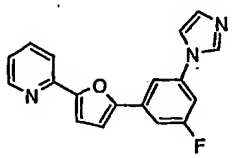
B258



In a similar fashion, a solution of 3-bromo-2-(3-cyanophenyl)-furan (98.04 mg, 0.395 mmol), 5-chloro-pyridyl 2-trimethyl stannane (170 mg, 0.35 mmol) and $Pd(PPh_3)_4$ (20 mg, 0.02 mmol) in anhydrous toluene (5 mL) was stirred at 110°C for 3 days. After cooling to room temperature, the product was filtered through 1g SPE tube and washed through with dichloromethane (50mL), and the solvent was removed *in vacuo*. Chromatography (5g silica SPE tube, 10% ethyl acetate in hexanes) yielded 5.9 mg (7.3%, GC/MS RT 9.876 min., 100%pure) of 3-(5-chloro-2-pyridyl)-2-(3-cyanophenyl)-furan. ^{1}H-NMR ($CDCl_3$), δ (ppm): 8.56 (d, 1H), 8.06 (s, 1H), 8.00 (s, 1H), 7.92 (d, 1H), 7.57 (d_{AB}, 1H), 7.53 (d_{AB}, 3H), 7.46 (d, 1H), 7.23 (s, 1H).

2-(2-Pyridyl)-5-(5-fluoro-3-(1-imidazolyl)phenyl)-furan

B259



Intermediates: 5-Bromo-2-(2-pyridyl)-furan

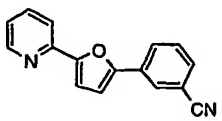
N-Bromosuccinimide (187 mg, 1.05 mmol) and p-toluensulfonic acid (11 mg) were added to a solution of 2-pyridyl-2-furan (150 mg, 1.03 mmol) in benzene (12.5 mL) under argon. The resulting solution was stirred at 80 °C for 2 h. After cooling to room temperature, the product was washed sequentially with aqueous sodium sulfite (3 x 5mL), water (5 mL) and brine (5 mL), and dried by passing through an EX-TUBE (3 mL), using additional solvent (dichloromethane) to rinse. Chromatography (5g silica gel SPE tube, 70-100% dichloromethane in hexane)

afforded 180 mg (69% based on 88% purity by GC/MS) of 5-bromo-2-(2-pyridyl)-furan as a light brown oil. 1-(3-bromo-5-fluoro-phenyl)-*1H*-imidazole : 1-Bromo-3,5-difluorobenzene (1.78 mL, 15.5 mmol) was added to a solution of imidazole (1.07 g, 15.7 mmol) and potassium carbonate (2.2 g, 15.9 mmol) in DMF (20 mL). The resulting mixture was stirred at 110 °C for 36 h. After cooling to room temperature, water (75 mL) was added and the product was extracted into ethyl acetate (3 x 150 mL). The organic layer was washed sequentially with water (3 x 100 mL) and brine (100 mL) and dried over sodium sulfate. The solvent was removed *in vacuo* to afford 2.35 g of the crude product, which was contaminated with 5-bromo-1,3-bis(1-imidazolyl)benzene. A 320 mg portion of the product was further purified by chromatography (5g silica gel SPE tube, 1-5% methanol in dichloromethane) afforded 193.6 mg (38%) of 1-(3-bromo-5-fluoro-phenyl)-*1H*-imidazole.

Title compound synthesis: $Pd(PPh_3)_4$ (10 mg, 0.009 mmol) was added to a solution of hexamethylditin (169 mg, 0.52 mmol) and 5-bromo-2-(2-pyridyl)-furan (90 mg, 88% purity, 0.36 mmol) in toulene (2 mL) under argon. The resulting solution was stirred at 80 °C for 19 h. After cooling to room temperature, a second portion of $Pd(PPh_3)_4$ (10 mg, 0.009 mmol) and 1-(3-bromo-5-fluoro-phenyl)-*1H*-imidazole (86 mg, 0.36 mmol) were added and the resulting solution was stirred at 110 °C for 36 h. After cooling to room temperature, the solvent was removed *in vacuo*. Chromatography (5g silica gel SPE tube, 0-3% methanol in 1:1 chloroform:ethyl acetate) afforded 72.3 mg (66%) of 2-(2-pyridyl)-5-(5-fluoro-3-(1-imidazolyl)phenyl)-furan. ^{1}H-NMR ($CDCl_3$), δ (ppm): 8.63 (d, 1H), 7.93 (s, 1H), 7.78 (m, 2H), 7.57 (s, 1H), 7.45 (m, 1H), 7.35 (s, 1H), 7.23 (m, 3H), 7.03 (m, 1H), 6.91 (d, 1H).

3-(5-(2-pyridyl)-2-furyl)-benzonitrile

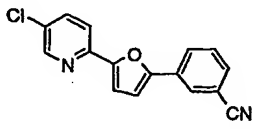
B260



Similarly, $Pd(PPh_3)_4$ (22 mg, 0.019 mmol) was added to a solution of 3-(5-bromofuran-2-yl)-benzonitrile (35 mg, 0.14 mmol) and 2-tributylstannylpyridine (71 mg, 0.19 mmol) in toluene (2 mL) under argon. In a similar manner, benzylbis(triphenylphosphine)palladium(II) chloride (10.5 mg, 0.014 mmol) was added to a solution of 3-(5-bromofuran-2-yl)-benzonitrile (35 mg, 0.14 mmol) and 2-tributylstannylpyridine (75 mg, 0.20 mmol) in toluene (2 mL) under argon. Both solutions were stirred at 110 °C for 18 h. After cooling to room temperature, the mixtures were combined since TLC of both reactions proved to be identical. The solvent was removed *in vacuo* from the combined product. Chromatography (5g silica gel SPE tube, dichloromethane) followed by triturating with 10% ethyl acetate in hexanes afforded 26.2 mg (38%) of 3-(5-(2-pyridyl)-2-furyl)-benzonitrile. ^{1}H-NMR ($CDCl_3$), δ (ppm): 8.63 (d, 1H), 8.05 (s, 1H), 7.96 (d, 1H), 7.77 (m, 3H), 7.54 (m, 2H), 7.20 (m, 1H), 6.89 (d, 1H).

3-(5-(5-choro-2-pyridyl)-2-furyl)-benzonitrile

B261

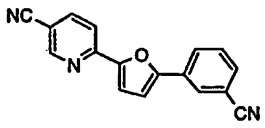


$Pd(PPh_3)_4$ (5 mg, 0.004 mmol) was added to a solution of hexamethylditin (160 mg, 0.49 mmol) and 5-chloro-2-bromopyridine (76 mg, 0.395 mmol) in toulene (1 mL) under argon. The resulting solution was stirred at 80 °C for 16 h. After cooling to room temperature, a second portion of $Pd(PPh_3)_4$ (20 mg, 0.019 mmol) and 3-(5-bromofuran-2-yl)-benzonitrile (79 mg, 0.32 mmol) were added and the resulting solution was stirred at 110 °C for 14 h. After cooling to room temperature, the solvent was removed *in vacuo*. Chromatography (5g silica gel SPE tube, 25-50% chloroform in hexane to 2% ethyl acetate in 1:1 chloroform:hexane) followed by triturating with hexanes and purification by preparative TLC (90% dichloromethane in hexane) afforded 15.7 mg (17%) of 3-(5-(5-choro-2-pyridyl)-2-furyl)-benzonitrile (97.5% pure by GC/MS, contaminated with

2.5% dimer). ^{1}H-NMR ($CDCl_3$), δ (ppm): 8.55 (d, 1H), 8.03 (s, 1H), 7.94 (dd, 1H), 7.73 (s, 2H), 7.54 (m, 12), 7.16 (d, 1H), 6.88 (d, 1H).

3-(5-(5-cyano-2-pyridyl)-2-furyl)-benzonitrile

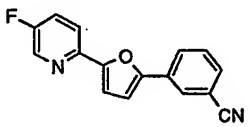
B262



In a similar fashion, $Pd(PPh_3)_4$ (10 mg, 0.009 mmol) was added to a solution of 2-trimethylstannyl-5-cyano-pyridine (22.7 mg, 0.085 mmol) and 3-(5-bromofuran-2-yl)-benzonitrile (31 mg, 0.125 mmol) in toluene (1 mL) under argon. The resulting solution was stirred at 110 °C for 15 h. After cooling to room temperature, the solvent was removed *in vacuo.* Chromatography (5g silica gel SPE tube, 50% chloroform in hexane to 20% ethyl acetate in 1:1 chloroform:hexane) followed by triturating with 50% dichloromethane in hexane afforded 5.3 mg (23%) of 3-(5-(5-cyano-2-pyridyl)-2-furyl)-benzonitrile (91% pure by GC/MS, contaminated by 9% dimer). ^{1}H-NMR ($CDCl_3$), δ (ppm): 8.85 (s, 1H), 7.87-8.05 (m, 5H), 7.52-7.63 (m, 3H), 7.36 (d, 1H), 6.95 (d, 1H), dimer impurity caused peak intensity to increase in region 8.00, 7.92, 7.49-7.57, plus 2 peaks additional peaks exactly overlapping with pure dimer @ δ (ppm): 6.87 (d) & 6.80 (d).

3-(5-(5-fluoro-2-pyridyl)-2-furyl)-benzonitrile

B263

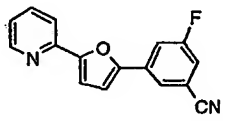


In a similar fashion, $Pd(PPh_3)_4$ (25 mg, 0.022 mmol) was added to a solution of hexamethylditin (163 mg, 0.50 mmol) and 5-fluoro-2-bromopyridine (87 mg,

0.49 mmol) in toulene (4 mL) under argon. The resulting solution was stirred at 80 °C for 15 h. After cooling to room temperature, a second portion of $Pd(PPh_3)_4$ (25 mg, 0.022 mmol) and 3-(5-bromofuran-2-yl)-benzonitrile (105 mg, 0.42 mmol) were added and the resulting solution was stirred at 110 °C for 48 h. After cooling to room temperature, the mixture was diluted with dichloromethane and passed through a 1g silica gel SPE tube using dichloromethane to elute the product. Flash chromatography (silica gel, 50-100% dichloromethane in hexane) afforded 48.4 mg (43%) of 3-(5-(5-fluoro-2-pyridyl)-2-furyl)-benzonitrile (pure by GC/MS). ^{1}H-NMR ($CDCl_3$), δ (ppm): 8.48 (d, 1H), 8.03 (s, 1H), 7.95 (m, 1H), 7.81 (m, 1H), 7.51 (m, 3H), 7.11 (d, 1H), 6.87 (d, 1H).

3-Fluoro-5-(5-(2-pyridyl)-2-furyl)-benzonitrile

B264



3-(5-Bromofuran-2-yl)-5-fluoro-benzonitrile intermediate: In a similar fashion, 3-(5-Bromofuran-2-yl)-5-fluoro-benzonitrile was prepared from N-bromosuccinimide (123 mg, 0.69 mmol), p-toluensulfonic acid (8 mg) and 3-furan-2-yl-benzonitrile (128 mg, 0.68 mmol) in benzene (10 mL) at 80 °C for 2.5 h. Standard workup and chromatography (5g silica gel SPE tube, 2.5-5% ethyl acetate in hexane) afforded 181 mg (86% based on 86% purity by GC/MS) of 3-(5-bromofuran-2-yl)-5-fluoro-benzonitrile.

$Pd(PPh_3)_4$ (10 mg, 0.009 mmol) was added to a solution of 3-(5-bromofuran-2-yl)-5-fluoro-benzonitrile (180 mg, 86% purity, 0.59 mmol) and 2-trimethylstannylpyridine (193 mg, 0.80 mmol) in toluene (2.5 mL) under argon. The resulting solution was stirred at 110 °C for 48 h. After cooling to room temperature, the solvent was removed *in vacuo.* Flash chromatography (silica gel, 35-100% dichloromethane in hexane) afforded 67.7 mg (43%) of 3-fluoro-5-(5-(2-pyridyl)-2-furyl)-benzonitrile. ^{1}H-NMR ($CDCl_3$), δ (ppm): 8.64 (d, 1H), 7.76-7.83 (m, 3H), 7.66 (m, 1H), 7.24 (m, 2H), 7.19 (d, 1H), 6.92 (d, 1H).

Example 10

Oxazoles via Oxazolone intermediate

General Synthesis of 3-Cyano-5-substituted benzamides:

To a mixture of aqueous ammonium hydroxide and ethylacetate (ratio of 1: 5) at 0°C was added slowly the benzoyl chloride (also prepared from the acid and oxalyl chloride). The mixture was stirred at room temperature for 15 minutes after which the ethylacetate layer was seperated. The aqueous layer was extracted vigorously with ethylacetate, the combined organic layer was washed with brine, dried over anhydrous Na_2SO_4 and concentrated in vacuo to give the product.

General Synthesis of the 2-Aryloxazolones:

To a solution of the benzamide in 1,2-dichloroethane was added oxalyl chloride (4-5 equivalents) and the mixture was heated to reflux for 18 h. The solvent was removed in vacuo and the crude acyl isocyanates dissolved in dry ether and diazomethane (prepared from N-methyl-N-nitrosourea and 50% aqueous KOH) in ether was added from a dropping funnel very slowly until the bubbling ceases. The mixture was then filtered to give the 2-aryloxazolone.

General Synthesis of the 2-Aryl-4-trifluoromethanesulphonyloxy-1,3-oxazole:

To a solution of the 2-Aryloxazolone and 2,6-lutidine (2 eqv.) in CH_2Cl_2 at 0°C was added triflic anhydride (1.5 eqv.) dropwise over 15 minutes. The mixture was allowed to come to room temperature and stirred overnight. The solvent was removed in vacuo and then purified by flash column chromatography on silica gel with CH_2Cl_2 as eluant

General synthesis of 2-Aryl-4-pyrid-2-yl-1,3-oxazoles:

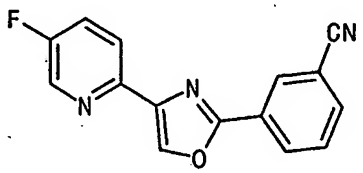
To a mixture of 2-Aryl-4-trifluoromethanesulphonyloxy-1,3-oxazole, LiCl, and 2-trimethylstannylpyridine in dioxane under argon was added $Pd(PPh_3)_4$ and the

mixture was heated to 100°C overnight. After cooling to room temperature, the solvent was removed in vacuo and the residue was purified by flash column chromatography on silica gel to afford the final product.

Thus, using the general method for synthesis of oxazoles via oxazolone intermediate the following compounds were obtained:

2-(3-cyanophenyl)-4-(5-Fluoropyrid-2-yl)-1,3-oxazole

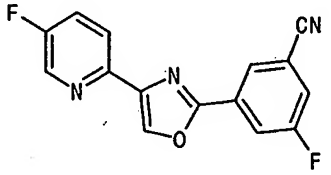
B265



2-(3-cyanophenyl)-4-(5-Fluoropyrid-2-yl) -1,3-oxazole (an off-white solid, 180 mg, 72% yield); 1HNMR(CDCl3) δ: 8.48 (d, 1H), 8.41 (s,1H), 8.35 (m,1H), 8.30 (m, 1H), 8.00 (dd, 1H), 7.75 (m, 1H), 7.62 (t, 1H), 7.52 (dt, 1H).

2-(3-cyano-5-fluorophenyl)-4-(5-Fluoropyrid-2-yl)-1,3-oxazole

B266

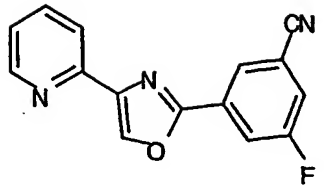


2-(3-cyano-5-fluorophenyl)-4-(5-Fluoropyrid-2-yl)-1,3-oxazole (a white solid, 65 mg, 55% yield); 1HNMR(CDCl3) δ: 8.48 (d, 1H), 8.31 (s,1H), 8.23 (d,1H), 8.07 (m, 1H), 8.00 (dd, 1H), 7.52 (m, 1H), 7.46 (m, 1H).

2-(3-cyano-5-fluoro

phenyl)-4-(2-pyridyl)-1,3-oxazole

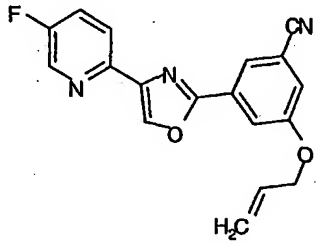
B267



2-(3-cyano-5-fluorophenyl)-4-(2-pyridyl) -1,3-oxazole (a white solid, 75 mg, 65% yield); 1HNMR(CDCl3) □: 8.62 (d, 1H), 8.38 (s,1H), 8.23 (s,1H), 8.07 (m, 1H), 8.00 (d, 1H), 7.80 (dt, 1H), 7.46 (m, 1H), 7.24 (m, 1H).

2-(5-allyloxy-3-cyanophenyl)-4-(5-Fluoropyrid-2-yl)-1,3-oxazole

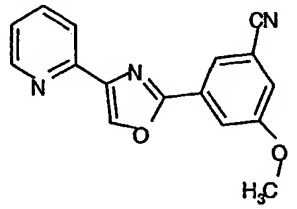
B268



2-(5-allyloxy-3-cyanophenyl)-4-(5-Fluoropyrid-2-yl) -1,3-oxazole (an off white solid, 11 mg, 15% yield); 1HNMR(CDCl3) □: 8.47 (d, 1H), 8.28 (s,1H), 7.99 (m, 2H), 7.86 (s, 1H), 7.51 (m, 1H), 7.24 (s, 1H), 6.05 (m, 1H), 5.40 (m, 2H), 4.65 (d, 2H).

2-(3-cyano-5-methoxyphenyl)-4-(pyrid-2-yl)-1,3-oxazole

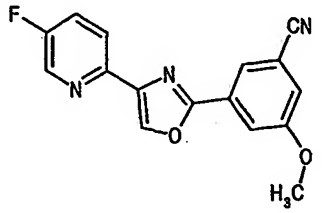
B269



2-(3-cyano-5-methoxyphenyl)-4-(pyrid-2-yl) -1,3-oxazole (a white solid, 600 mg, 65% yield); 1HNMR(CDCl3) □: 8.62 (d, 1H), 8.34 (s,1H), 7.92 (m, 2H), 7.84 (s, 1H), 7.78 (m, 1H), 7.78 (t, 1H), 7.25 (t, 1H), 3.94 (s, 3H).

2-(3-cyano-5-methoxyphenyl)-4-(5-Fluoropyrid-2-yl)-1,3-oxazole

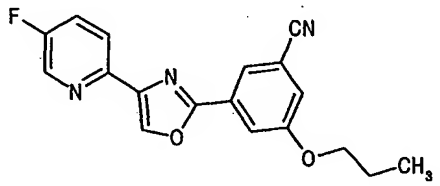
B270



2-(3-cyano-5-methoxyphenyl)-4-(5-Fluoropyrid-2-yl) -1,3-oxazole (a white solid, 35 mg, 35% yield); 1HNMR(CDCl3) □: 8.47 (d, 1H), 8.29 (s,1H), 8.02 (d,1H), 7.99 (s, 1H), 7.85 (s, 1H), 7.50 (m, 1H), 7.24 (s, 1H), 3.93 (s, 3H).

2-(3-cyano-5-n-propyloxyphenyl)-4-(5-Fluoropyrid-2-yl)-1,3-oxazole

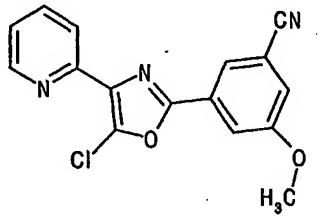
B271



2-(3-cyano-5-n-propyloxyphenyl)-4-(5-Fluoropyrid-2-yl) -1,3-oxazole (a white solid, 430 mg, 55% yield) 1HNMR(CDCl3) □: 8.46 (d, 1H), 8.27 (s,1H), 8.00 (m,1H), 7.95 (s, 1H), 7.83 (s, 1H), 7.50 (m, 1H), 7.23 (s, 1H), 4.02 (t, 3H), 1.85 (m, 1H), 1.07 (t, 3H).

2-(3-cyano-5-methoxyphenyl)-4-(pyrid-2-yl)-5-chloro-1,3-oxazole

B272



N-chlorosuccinimide (32 mg, 0.24 mmol) and benzoyl peroxide (4.6 mg, 0.019 mmol) were added to a solution of 2-(3-cyano-5-methoxyphenyl)-4-(5-pyrid-2-yl)-1,3-oxazole (52 mg, 0.19mmol) in carbon tetrachloride (2 mL). The reaction was

heated at 80 °C for 4 hours. The solvent was removed *in vacuo* and the compound was purified by eluting through and 5g SPE tube with a gradient of 5-10% ethyl acetate in hexanes. 2-(3-cyano-5-methoxyphenyl)-4-(pyrid-2-yl)-5-chloro-1,3-oxazole was afforded as a white solid (30 mg, 51% yield). 1HNMR(CDCl3) □: 8.75 (d, 1H), 8.03 (d,1H), 7.97 (s,1H), 7.82 (m, 2H), 7.29 (d, 2H), 3.93 (s, 3H).

EXAMPLE 11: Assay of Group I receptor antagonist activity

Primary astrocyte cultures were prepared from 3-5 day old Sprague-Dawley rat pups using a modification of Miller (Miller *et al, J. Neuroscience, 15(9):* 6103-6109, 1995). In brief, primary cultures were plated on poly-L lysine coated flasks in Dulbecco's modified Eagle's medium (DMEM) containing fetal calf serum (FCS). After 6 days, cell cultures were shaken over night at 280 rpm, then transferred to astrocyte-defined media (ADM) containing growth factors that up-regulate the expression of mGluR5 (Miller et al., 1995). For cuvette analysis, cultures were up-regulated with growth factors in flasks for 3-5 days, then harvested and prepared for measurement of $[Ca^{2+}]_i$ mobilization as previously described (Nemeth et al., 1998).

For FLIPR analysis, cells were seeded on poly-D lysine coated clear bottom 96-well plates with black sides and analysis of $[Ca^{2+}]_i$ mobilization was performed 3 days following the growth factor up-regulation. Cell cultures in the 96-well plates were loaded with a 4 μM solution of acetoxymethyl ester form of the fluorescent calcium indicator fluo-3 (Molecular Probes, Eugene, Oregon) in 0.01% pluronic. All assays were performed in a buffer containing 127 mM NaCl, 5 mM KCl, 2 mM $MgCl_2$, 0.7 mM NaH_2PO_4, 2 mM $CaCl_2$, 0.422 mg/ml $NaHCO_3$, 2.4 mg/ml HEPES, 1.8 mg/ml glucose and 1 mg/ml BSA Fraction IV (pH 7.4).

FLIPR experiments were done using a laser setting of 0.800 W and a 0.4 second CCD camera shutter speed. Each FLIPR experiment was initiated with 180 μL of buffer present in each well of the cell plate. A 20 μL addition from the antagonist plate was followed by a 50 μL addition from the agonist plate. After

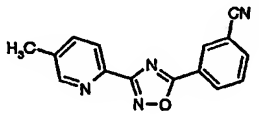
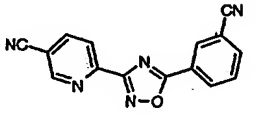
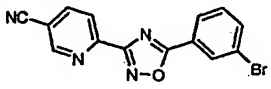
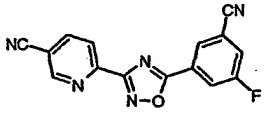
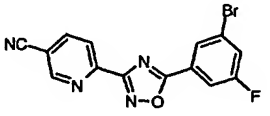
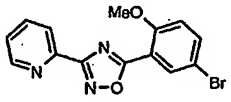
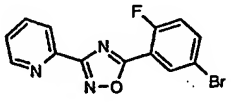
each addition the fluorescence signal was sampled 50 times at 1 second intervals followed by 3 samples at 5 second intervals. Responses were measured as the peak height of the response within the sample period.

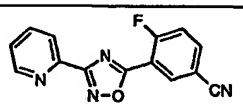
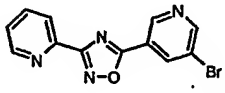
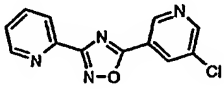
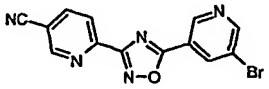
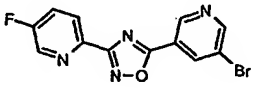
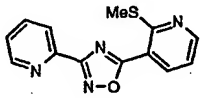
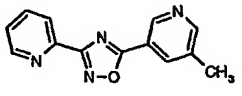
EC_{50}/IC_{50} determinations were made from data obtained from 8 point concentration response curves (CRC) performed in duplicate. Agonist CRC were generated by scaling all responses to the maximal response observed for the plate. Antagonist block of the agonist challenge was normalized to the average response of the agonist challenge in 14 control wells on the same plate. Compounds of the present invention antagonized mGluR5 as determined by their IC_{50} values which fell into the range of 11 – 9140 nM.

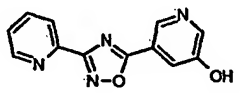
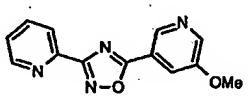
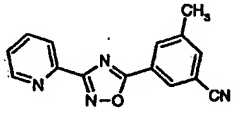
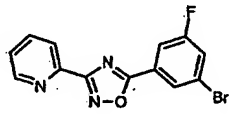
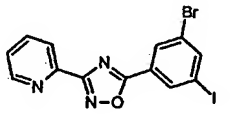
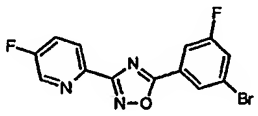
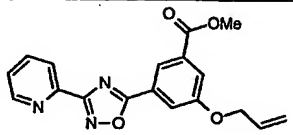
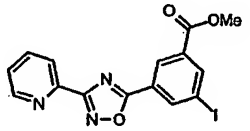
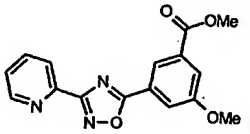
The invention thus has been disclosed broadly and illustrated in reference to representative embodiments described above. Those skilled in the art will recognize that various modifications can be made to the present invention without departing from the spirit and scope thereof.

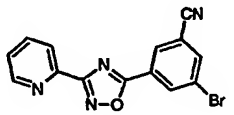
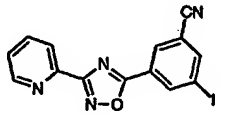
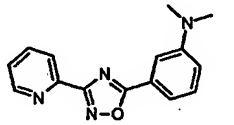
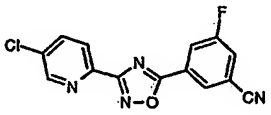
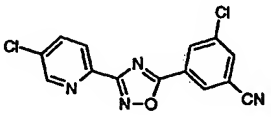
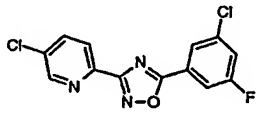
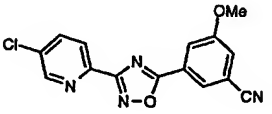
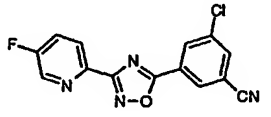
WHAT IS CLAIMED IS:

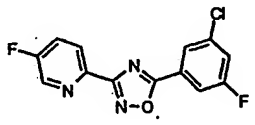
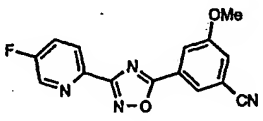
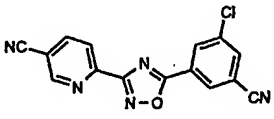
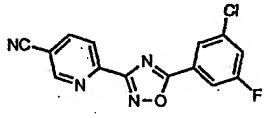
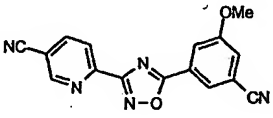
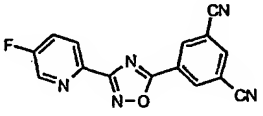
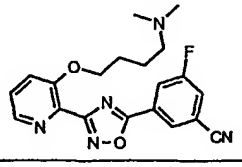
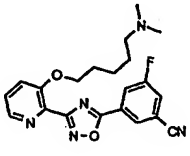
1. A compound, or a pharmaceutically acceptable salt thereof, selected from the group consisting of compounds as set forth in the following table:

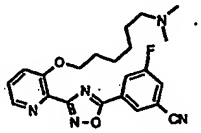
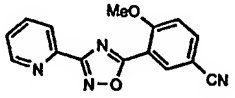
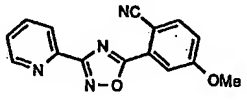
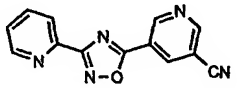
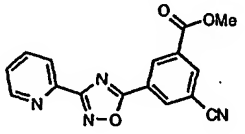
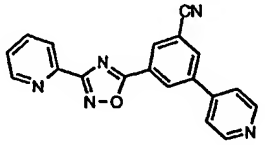
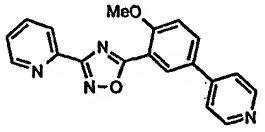
B57	
B58	
B59	
B60	
B61	
B62	
B63	

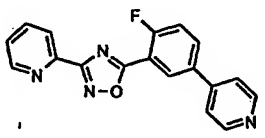
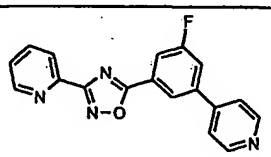
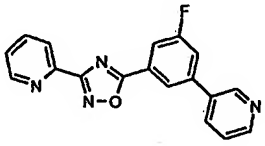
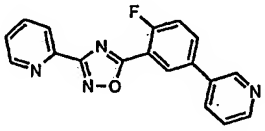
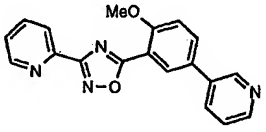
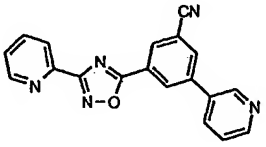
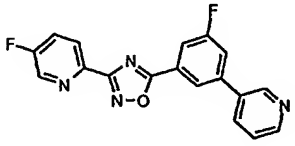
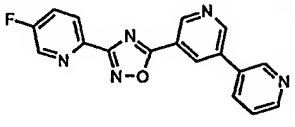
B64	
B65	
B66	
B67	
B68	
B69	
B70	

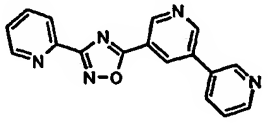
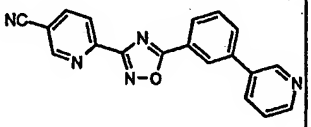
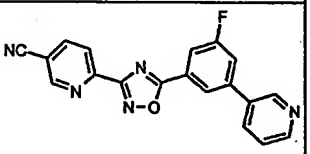
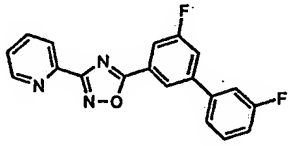
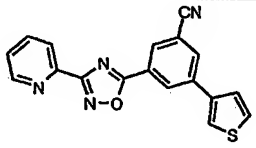
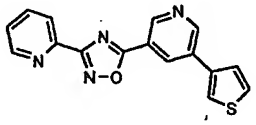
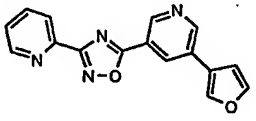
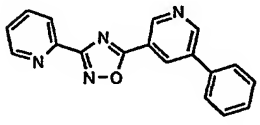
B71	
B72	
B73	
B74	
B75	
B76	
B77	
B78	
B79	

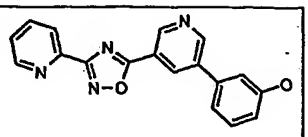
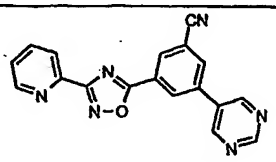
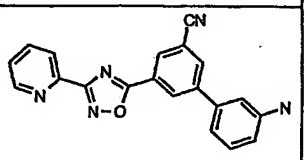
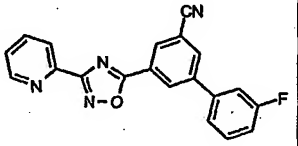
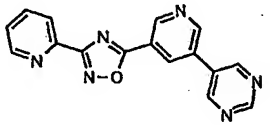
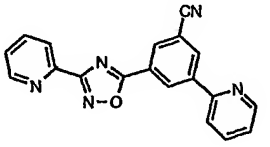
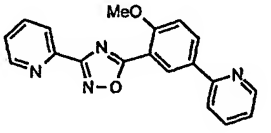
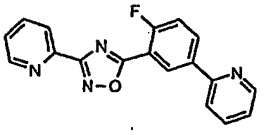
B80	
B81	
B82	
B83	
B84	
B85	
B86	
B87	

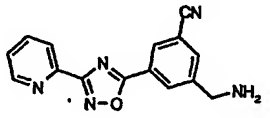
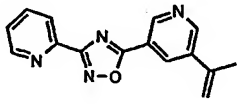
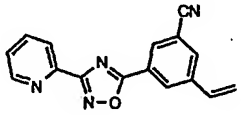
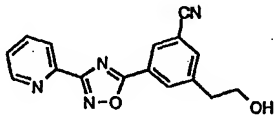
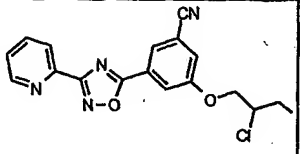
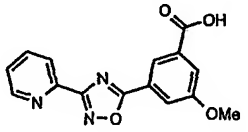
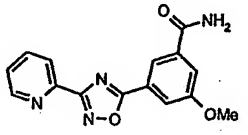
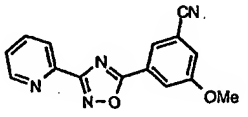
B88	
B89	
B90	
B91	
B92	
B93	
B94	
B95	

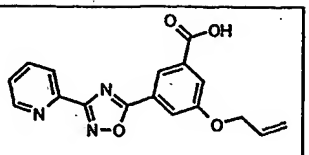
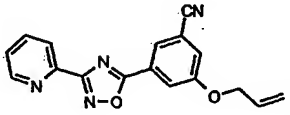
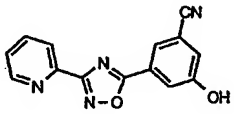
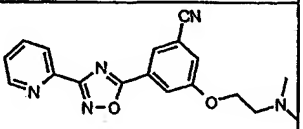
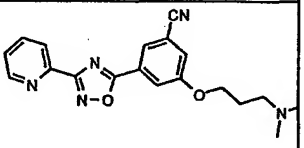
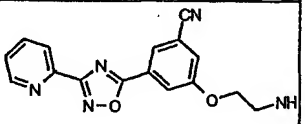
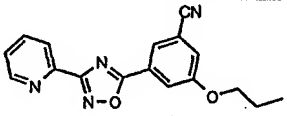
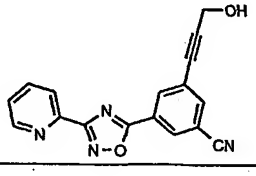
B96	
B97	
B98	
B99	
B100	
B101	
B102	

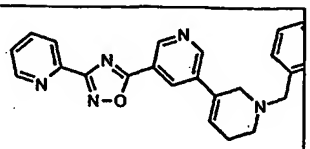
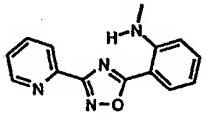
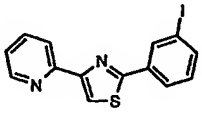
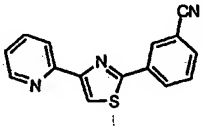
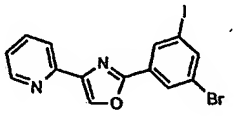
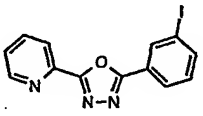
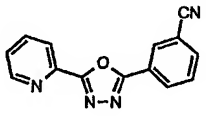
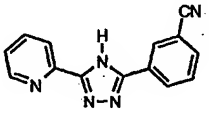
B103	
B104	
B105	
B106	
B107	
B108	
B109	
B110	

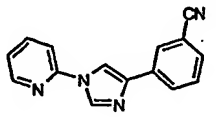
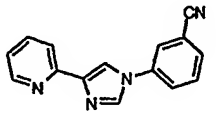
B111	
B112	
B113	
B114	
B115	
B116	
B117	
B118	

B119	
B120	
B121	
B122	
B123	
B124	
B125	
B126	

B127	
B128	
B129	
B130	
B131	
B132	
B133	
B134	

B135	
B136	
B137	
B138	
B139	
B140	
B141	
B142	

B143	
B144	
B145	
B146	
B147	
B148	
B149	
B150	

B151	
B152	

2. A pharmaceutical composition comprising a therapeutically effective, non-toxic, amount of a compound of claim 1 and a pharmaceutically acceptable carrier.

3. A method for treating a disease associated with Group I mGluR activation comprising the step of administering to a patient in need of such treatment a pharmaceutical composition as defined in claim 2.

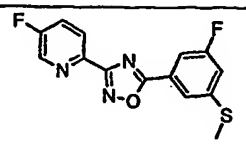
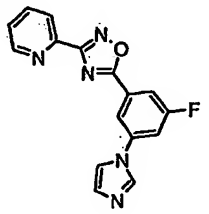
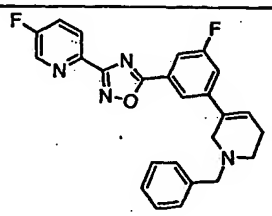
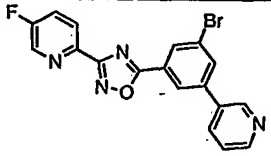
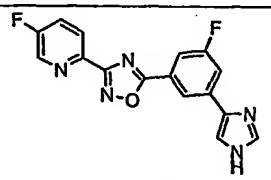
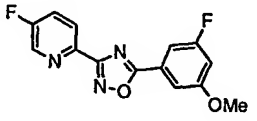
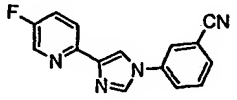
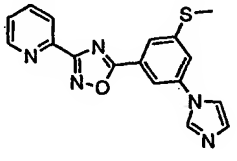
4. A method according to claim 3 wherein the disease is a disease associated with mGluR activation.

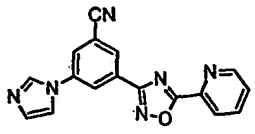
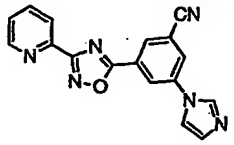
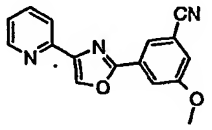
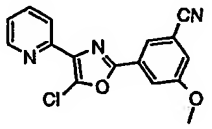
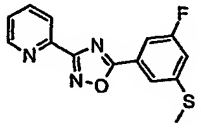
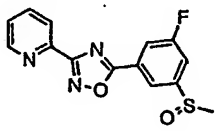
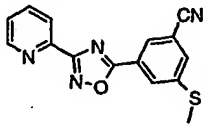
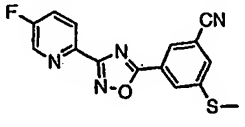
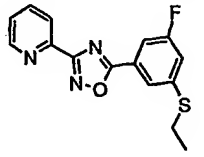
5. A method according to claim 4 wherein the disease is a neurological disease.

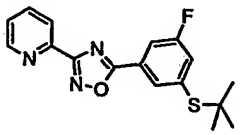
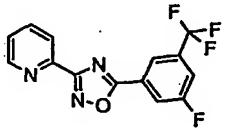
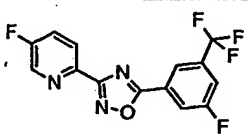
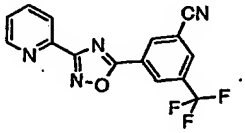
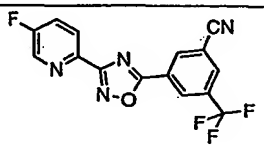
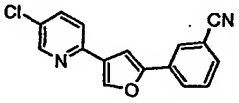
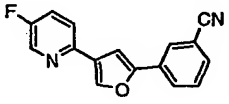
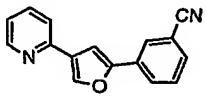
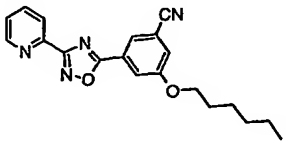
6. A method according to claim 4 wherein the disease is a psychiatric disease.

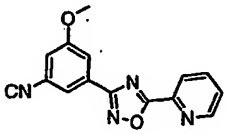
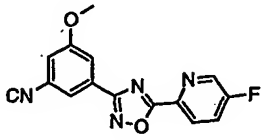
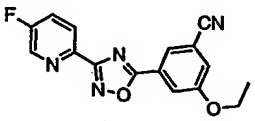
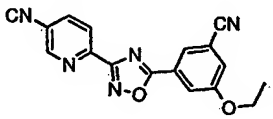
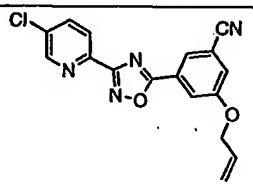
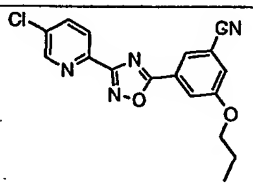
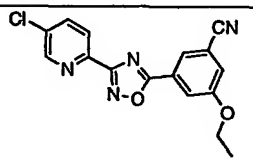
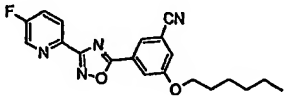
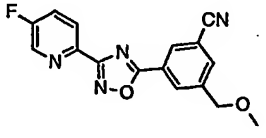
7. A method according to claim 4 wherein the disease is selected from the group consisting of stroke, head trauma, anoxic injury, ischemic injury, hypoglycemia, epilepsy, pain, migraine headaches, Parkinson's disease, senile dementia, Huntington's Chorea, and Alzheimer's disease.

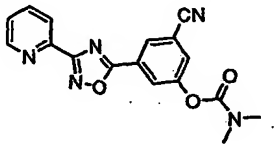
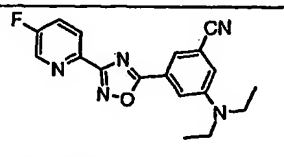
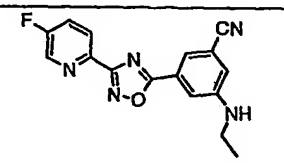
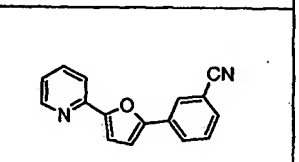
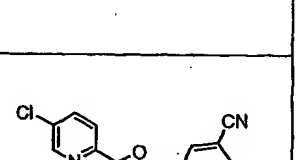
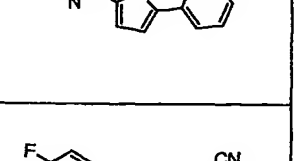
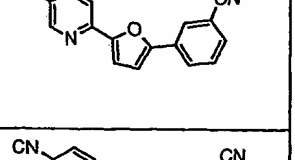
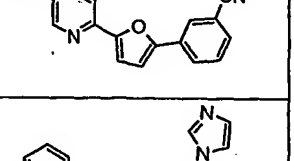
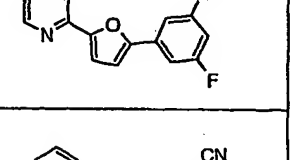
8. A compound, or a pharmaceutically acceptable salt thereof, selected from the group consisting of compounds as set forth in the following table:

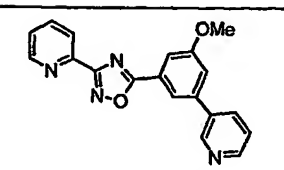
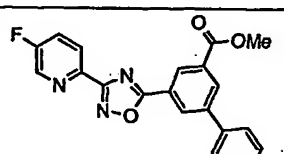
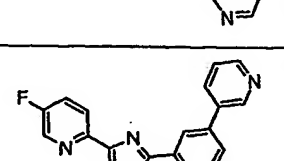
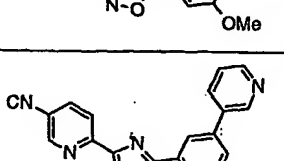
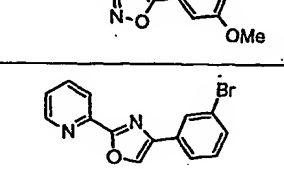
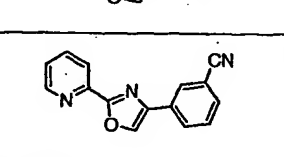
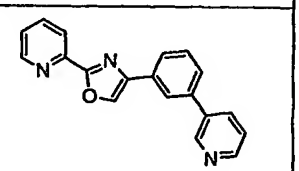
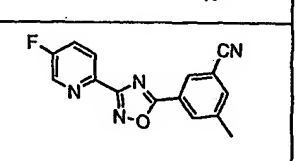
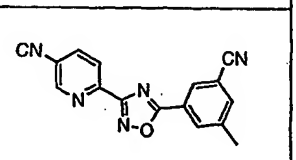
B153	
B154	
B250	
B212	
B251	
B213	
B252	
B253	

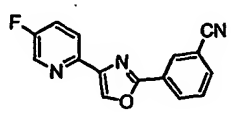
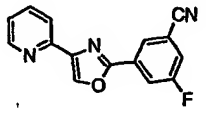
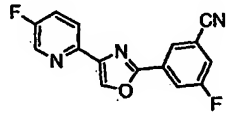
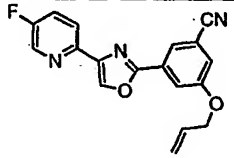
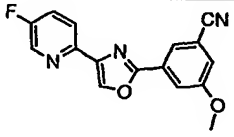
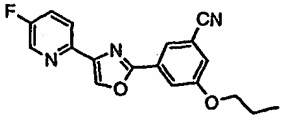
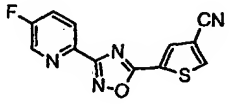
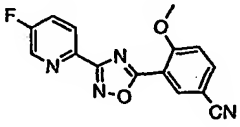
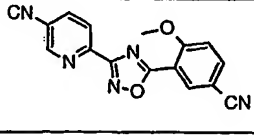
B254	
B255	
B269	
B272	
B216	
B217	
B214	
B215	
B218	

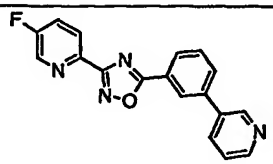
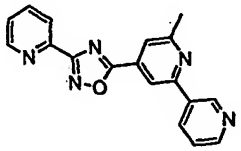
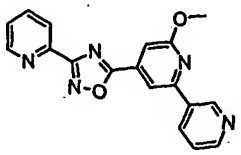
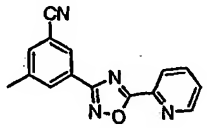
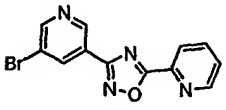
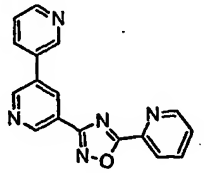
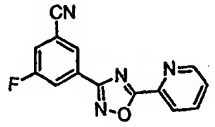
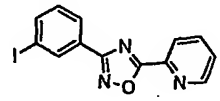
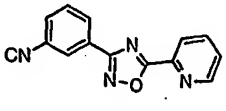
B219	
B155	
B156	
B223	
B224	
B258	
B257	
B256	
B244	

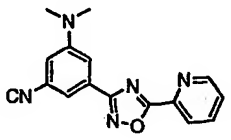
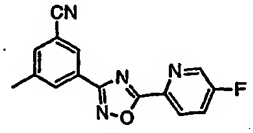
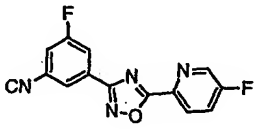
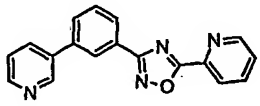
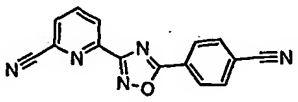
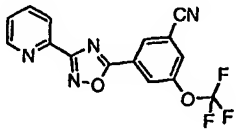
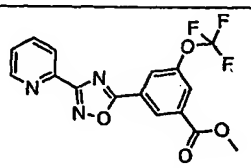
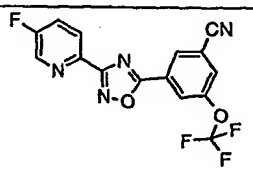
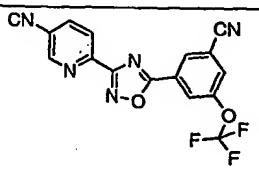
B167	
B168	
B169	
B170	
B171	
B172	
B173	
B174	
B175	

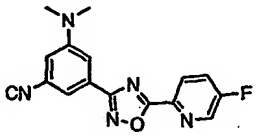
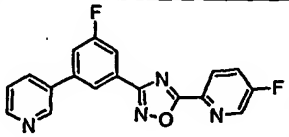
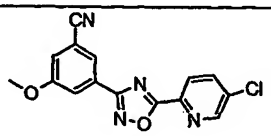
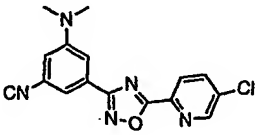
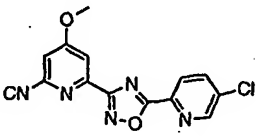
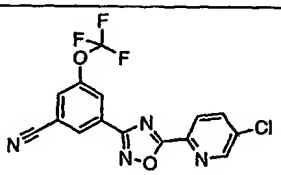
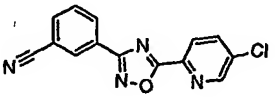
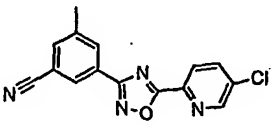
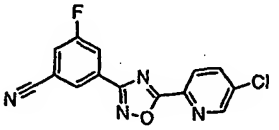
B245	
B246	
B247	
B260	
B261	
B263	
B262	
B259	
B264	

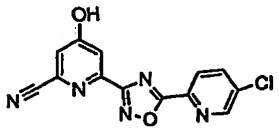
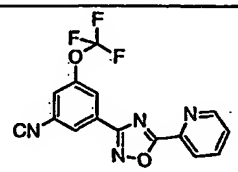
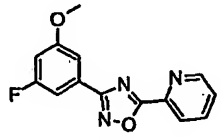
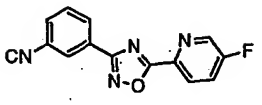
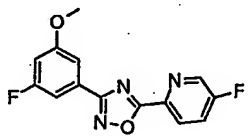
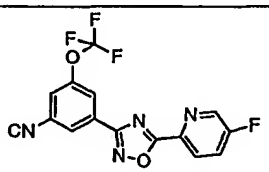
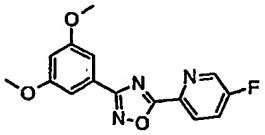
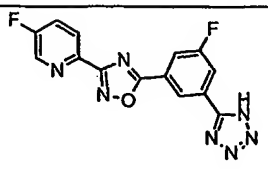
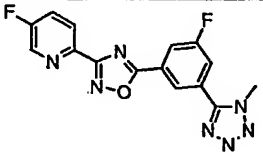
B274	
B275	
B276	
B277	
B278	
B279	
B280	
B220	
B221	

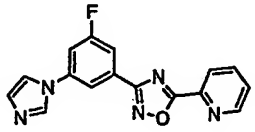
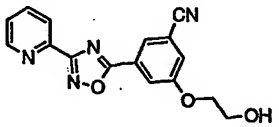
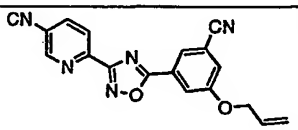
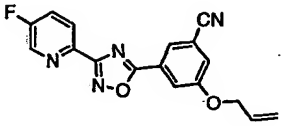
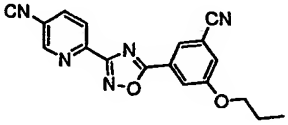
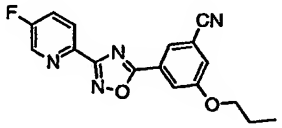
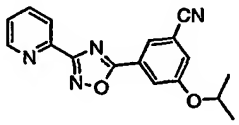
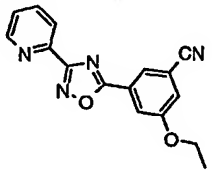
B265	
B267	
B266	
B268	
B270	
B271	
B222	
B176	
B177	

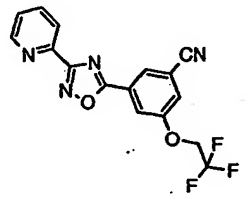
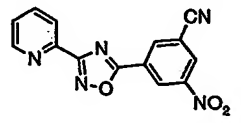
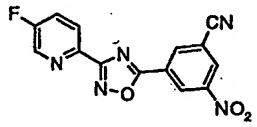
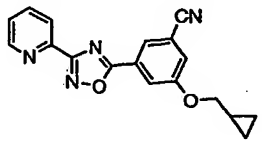
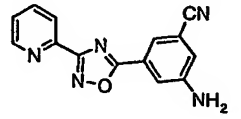
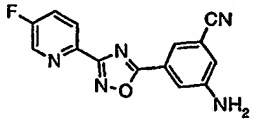
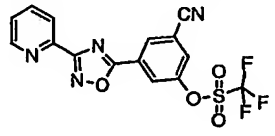
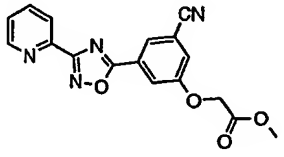
B225	
B226	
B227	
B181	
B182	
B228	
B183	
B184	
B186	

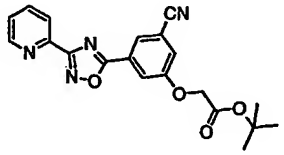
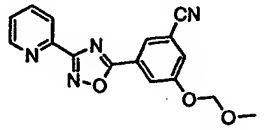
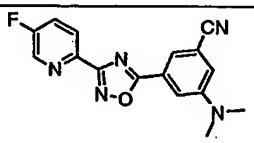
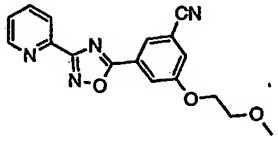
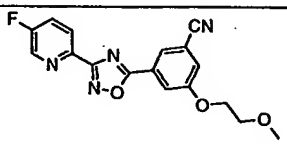
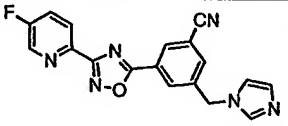
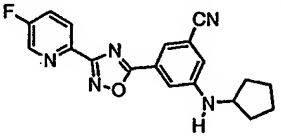
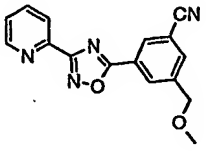
B187	
B188	
B189	
B229	
B190	
B191	
B192	
B193	
B194	

B195	
B230	
B197	
B196	
B198	
B200	
B201	
B202	
B203	

B199	
B204	
B205	
B206	
B208	
B207	
B209	
B248	
B249	

B210	
B231	
B157	
B158	
B159	
B160	
B232	
B233	

B234	
B161	
B162	
B235	
B236	
B237	
B238	
B239	

B240	
B241	
B163	
B242	
B164	
B165	
B243	
B166	

9. A pharmaceutical composition comprising a therapeutically effective, non-toxic, amount of a compound of claim 8 and a pharmaceutically acceptable carrier.

10. A method for treating a disease associated with Group I mGluR activation comprising the step of administering to a patient in need of such treatment a pharmaceutical composition as defined in claim 9.

11. A method according to claim 10 wherein the disease is a disease associated with mGluR activation.

12. A method according to claim 11 wherein the disease is a neurological disease.

13. A method according to claim 11 wherein the disease is a psychiatric disease.

14. A method according to claim 11 wherein the disease is selected from the group consisting of stroke, head trauma, anoxic injury, ischemic injury, hypoglycemia, epilepsy, pain, migraine headaches, Parkinson's disease, senile dementia, Huntington's Chorea, anxiety, and Alzheimer's disease.

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(75) Inventors/Applicants *(for US only)*: **VAN WAGENEN, Bradford** [US/US]; 3969 South 3250 East, Salt Lake City, UT 84127 (US). **STORMANN, Thomas, M.** [US/US]; 1327 East Harrison, Salt Lake City, UT 84105 (US). **MOE, Scott, T.** [US/US]; 6152 South Vinefield Lane, Salt Lake City, UT 84121 (US). **SHEEHAN, Susan, M.** [US/US]; 1803 East Redondo Avenue, Salt Lake City, UT 84108 (US). **MCLEOD, Donald, A.** [US/US]; 7740 South Newport Way, Salt Lake City, UT 84121 (US). **SMITH, Daryl, L.** [US/US]; 1592 East Parkridge Drive, Salt Lake City, UT 84121 (US). **ISAAC, Methvin, Benjamin** [CN/CA]; 1507-10 Markbrook Lane, Etobiocoke, Ontario M9V 5E3 (CA).

(74) Agents: **BENT, Stephen, A.** et al.; Foley & Lardner, 3000 K. Street, N.W., Washington, DC 20007-5109 (US).

(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW.

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Published:
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14 November 2002

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 02/068417 A3

(54) Title: HETEROPOLYCYCLIC COMPOUNDS AND THEIR USE AS METABOTROPIC GLUTAMATE RECEPTOR ANTAGONISTS

(57) Abstract: The present invention provides compounds and pharmaceutical compositions that act as antagonists at metabotropic glutamate receptors, and that are useful for treating neurological diseases and disorders. Method of preparing the compounds also are disclosed.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 02/04689

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D413/04 C07D413/10 C07D417/04 C07D401/04 C07D413/12
C07D405/04 C07D405/10 C07D413/14 A61K31/44 A61P25/18

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, PAJ

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,Y	WO 01 12627 A (NPS PHARMACEITICALS INC.) 22 February 2001 (2001-02-22) claims; examples	1-14
Y	WO 98 17652 A (BOEHRINGER INGELHEIM) 30 April 1998 (1998-04-30) page 60, line 1 -page 67, line 2; claims; examples	1-14
A	WO 99 02497 A (NOVARTIS ERFINDUNGEN) 21 January 1999 (1999-01-21) page 1 -page 2; claims; examples	1-14
A	US 3 647 809 A (HARSANYI ET. AL.) 7 March 1972 (1972-03-07) claims; examples	1-14

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

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"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
7 June 2002	21/06/2002

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Helps, I

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INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 02/04689

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 4 022 901 A (NARAYANAN ET. L.) 10 May 1977 (1977-05-10) claims; examples	1-14
A	M. OHKUBO ET. AL.: "Studies on cerebal Protective Agents. VII. Synthesis of Novel 4-Arylazole Derivatives with Anti-anoxic Activity" CHEMICALAND PHARMACEUTICAL BULLETIN, vol. 43, no. 6, June 1995 (1995-06), pages 947-54, XP002153139 Chart 2, Tables 1-3	1-14
A	W. PEI ET. AL.: "Convenient Synthesis of 2-Alkyl(Aryl)-4,5-diphenyloxazoles and 2-Alkyl(Aryl)-4-phenyloxazoles" SYNTHESIS , no. 9, - September 1998 (1998-09) pages 1298-304, XP002153138 table 4	1-14
A	C. MONTOLIU ET. AL.: "Activation of the Metabotropic Glutamate Receptor mGluR5 Prevents Glutamate Toxicity in Primary Cultures of cerebellar Neurons." JOURNAL OF PHARMACOLOGY AND EXPERIMENTAL THERAPEUTICS, vol. 281, no. 2, May 1997 (1997-05), pages 643-7, XP001079734 cited in the application whole article	1-14

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 02/04689

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 10-14 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 02/04689

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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